Unsupported Price Increase Report

2020 Assessment

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We would also like to thank Laura Cianciolo for her contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new information may emerge following the publication of this report that could potentially influence the assessment.

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List of Acronyms and Abbreviations Used in this Report

ACR	American College of Rheumatology
ADT	Androgen deprivation therapy
BLS	Bureau of Labor Statistics
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPI	Consumer price increase
CRPC	Castration-resistant prostate cancer
CSPC	Castration-sensitive prostate cancer
bDMARD	Biologic disease modifying antirheumatic drug
cDMARD	Conventional disease modifying antirheumatic drug
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
HAQ-DI	Health Assessment Questionnaire Disability Index
HR	Hazard ratio
IBS	Irritable bowel syndrome
ICER	Institute for Clinical and Economic Review
MDA	Minimal disease activity
NEDA	No Evident Disease Activity
NR	Not reported
NT-proBNP	N-terminal pro–B-type natriuretic peptide
OS	Overall survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Prostate-specific antigen
RCT	Randomized controlled trial
SE	Shared epitome status
SF-36	36-Item Short-Form Health Survey
TD	Traveler's diarrhea
TNF	Tumor necrosis factor
UPI	Unsupported price increase
US	United States
WAC	Wholesale acquisition cost

Executive Summary

The price of many existing drugs, both brand and generic, can increase substantially over time, and questions are frequently raised regarding whether these price increases are justified. State policymakers have been particularly active in seeking measures to address this issue.[1-3]

Despite these initiatives, there had been no systematic approach at a state or national level to determine whether certain price increases are justified by new clinical evidence or other factors. In 2017, the Institute for Clinical and Economic Review (ICER) sought and received funding from Arnold Ventures to develop ICER Unsupported Price Increase (UPI) Reports to determine whether new clinical evidence or other information has appeared that could support the price increases of those drugs with recent, substantial price increases that have had the largest impact on national drug spending. This is the second of these reports.

Following the methods from our prior report, we first obtained a list of the 100 drugs with the largest sales revenue in the previous calendar year (2019) in the United States (US); this information came from SSR Health, LLC, the health care division of SSR, LLC, an independent investment research firm. We then excluded from this list 67 drugs whose increase in wholesale acquisition cost (WAC) was not larger than twice the increase in the medical consumer price index (CPI). A detailed description of the entire UPI Protocol is available separately.

For each of the remaining 33 drugs, we estimated, where possible, the increase in spending in the US during 2018-2019 that was due to increases in net price as opposed to increases in volume. The intent was to select the top 10 drugs for further assessment; manufacturers of the identified top 10 drugs were asked for early input as to whether our figures on change in net price, sales volume, and overall net revenue were correct. After the cutoff date for informing ICER of corrections to net price had passed, the manufacturer of secukinumab (Cosentyx®, Novartis) provided information showing that it did not have an increase in net price. The 2020 UPI Protocol did not anticipate this situation, but based on the 2019 UPI Protocol, secukinumab was removed from the review. Also after the cutoff date, the manufacturer of enzalutamide (Xtandi®, Astellas) provided information showing that this drug would likely have been in position 11 on the list. Based on the 2019 UPI Protocol, enzalutamide was kept in the review. In addition, we received public input recommending we evaluate price increases for etanercept (Enbrel®, Amgen). Following our protocol, which allows for inclusion of up to three drugs that do not make the initial list, we added etanercept to the remaining nine drugs, creating the final list of 10 drugs for assessment. Once included, etanercept's increase in budget impact at the national level placed it in the top position on the list.

Assessments were then performed on these 10 drugs to determine whether there was new clinical evidence in the prior two years (2018 through 2019) that demonstrated "moderate/high quality

new evidence of a substantial improvement in net health benefit compared with what was previously believed." Drugs judged to have evidence that meets this standard are reported as having price increases "with new clinical evidence." To arrive at this judgment, ICER accepted and reviewed submissions from manufacturers and/or performed an independent systematic review of publicly available results from randomized controlled trials (RCTs). For drugs with multiple indications, evidence was sought for indications responsible for at least 10% of a drug's utilization. ICER reviewed the quality of the new evidence using the widely-accepted evidence grading system called GRADE.[4] For evidence that was felt to be high or moderate quality, ICER then assessed the magnitude of the additional net clinical benefit compared with what was previously believed.

Table ES1 on the following page shows the results of the evidence assessments for these 10 drugs. Seven were judged to have price increases unsupported by new clinical evidence and three were found to have price increases with new clinical evidence. The total increase in spending in the US over one year due to price increases for the seven drugs found to have unsupported price increases amounted to $1.2 billion. Etanercept was determined to be one of the drugs whose price increase was unsupported by new clinical evidence, and its cumulative price increases were estimated to have had the single largest impact on national drug spending among all drugs evaluated in this report. Our judgment for etanercept of whether there was new evidence of "substantial" improved comparative clinical effectiveness was challenging given varying interpretations among clinical experts in the US and internationally of the relevance of the findings of one new randomized trial. Further details are provided later in the report.

ICER does not currently have the capacity to perform full economic analyses in conjunction with the evaluation of clinical evidence for the drugs in its UPI Reports. Therefore, even though three drugs did have new clinical evidence, this UPI Report does not attempt to determine whether the price increases were fully justified by meeting a health-benefit price benchmark that might be determined by a formal cost-effectiveness analysis. Instead, our assessment focused on whether new evidence existed that *could* justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases, we hope we have taken an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases.

ICER received public comments from state policymakers suggesting that insulin be evaluated in the current UPI Report, and we include a section on these drugs. Of note, however, the UPI methodology is not well suited for medications like insulin that have not experienced recent major increases in net prices. In addition, with multiple insulin analogues on the market, the budget impact at the national level due to price increases for any single drug would be relatively small compared to drugs in other treatment areas.

We found that in 2019, seven of the top 10 insulin products had sales of over $500 million, and all 10 had sales of over $200 million. From 2018 to 2019, the list price (WAC) increased for five of

these products, four had level pricing, and one had a decline in list price. Among the five products with increases in WAC, four experienced increases at more than medical CPI for the same period. However, net price appears to have declined for nine of these products. Thus, the actual price paid by the health system for these products was generally lower in 2019 than in 2018.

While higher net prices are the most potent force in driving up insurance premiums, and are thus important to plan sponsors, payers, and all members of a health system, list prices have important implications for patients. For uninsured patients who may experience the full cost of list pricing, insulin may be unaffordable. And high list prices can lead many insured patients to experience financial toxicity as well because health benefits often require payment of deductibles or co-insurance linked to the list price instead of the net price.

Thus, overall, it appears that net prices for insulin generally declined between 2018 and 2019, while WAC largely stayed level or increased. The size of the WAC increases, when they occurred, were mostly substantially greater than medical inflation overall and creates risk for greater financial toxicity for patients despite lower prices for payers.

Table ES1. Assessment Results

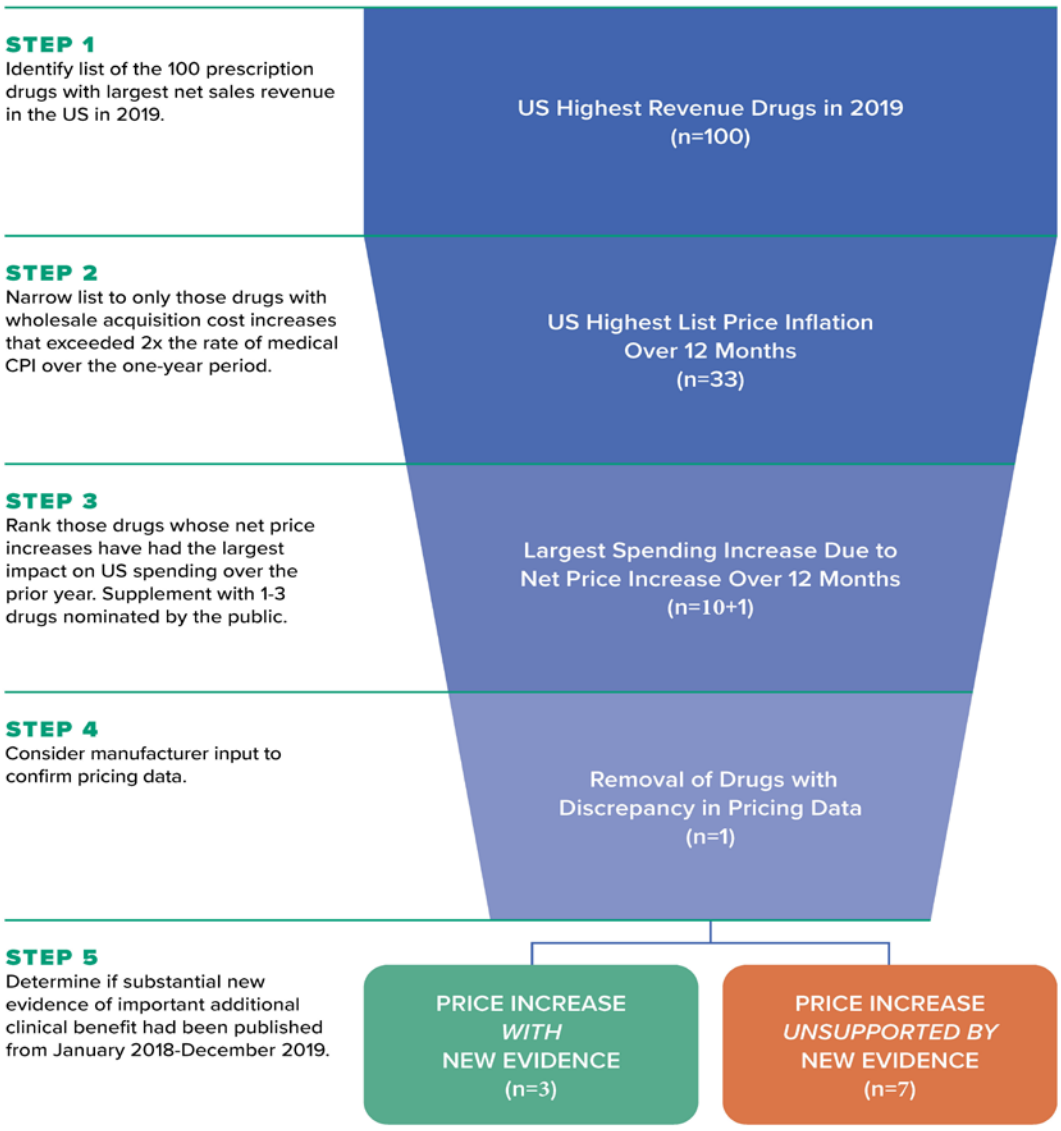
Drug	2018 to 2019 Percentage Change		Increase in Drug Spending at National Level Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Enbrel® (Etanercept)	5.4%	8.9%	$403
Invega Sustenna/Trinza® (Paliperidone Palmitate)	6.8%	10.7%	$203
Xifaxan® (Rifaximin)	8.4%	13.3%	$173
Orencia® (Abatacept)	6.0%	7.4%	$145
Tecfidera® (Dimethyl Fumarate)	6.0%	3.7%	$118
Humira® (Adalimumab)	6.2%	2.0%	$66
Vimpat® (Lacosamide)	7.0%	5.6%	$58
Drugs with Price Increases with New Clinical Evidence*			
Entresto® (Sacubitril/Valsartan)	9.6%	8.0%	$66
Entyvio® (Vedolizumab)	6.4%	2.3%	$48
Xtandi® (Enzalutamide)	5.9%	2.5%†	$37†

*This is not a determination that the new evidence necessarily justified these price increases.

†Revised estimates based on information Astellas provided on net price increase and increase in spending for Xtandi that was provided beyond the deadline in the protocol.

Figure ES1 on the following page shows the flow and process by which we selected the drugs for review.

Figure ES1. Drug Selection Process



As anticipated in the UPI Protocol, changes to the UPI procedures were made during this review and the experience of this review will influence changes in the protocol for the next UPI Report.

1. Introduction

The price of many existing drugs, both brand and generic, can increase substantially over time, and questions are frequently raised regarding whether these price increases are justified. State policymakers have been particularly active in seeking measures to address this issue.[1-3]

In 2019, the Institute for Clinical and Economic Review (ICER) published its first Unsupported Price Increase (UPI) Report after we organized a multi-stakeholder advisory group to provide input into the design of an approach for such reports. The advisory group was comprised of representatives from patient groups, drugmakers, and insurers representing Medicaid and the private market. The first report looked back at two years of price increases and three years of new evidence.

ICER again worked with this group to develop a revised UPI Protocol for the reports. Important changes for this year's report include changing the timeframe for price increases to one year (so as to have no overlap with prior UPI Reports) and for evidence to two years; an expanded definition of what evidence will be reviewed as new; and use of average prices for a given year to smooth out quarter-to-quarter variability.

ICER heard concerns from some members of the advisory group, as well as from other stakeholders, that UPI evaluations were being interpreted by some as suggesting that ICER believed most research done by manufacturers after drug launch was of little worth. We want to make it clear that this is completely incorrect. Research after drugs are on the market provides vital information, including information on safety, real-world effectiveness, how drugs should be used in certain subpopulations, confirmation of prior results, and insights into many other aspects of care. Investment by manufacturers in such research is critical to the advancement of medical knowledge. That does not mean, however, that the results of such research necessarily justify price increases that result in large increases in medical spending.

The annual UPI Report may evaluate up to 13 drugs that have experienced substantial price increases. As described in later sections, this year's UPI Report evaluated changes in the evidence base for 10 drugs and assessed whether there was potential evidentiary support for price increases.

It is important to note that ICER does not currently have the capacity to perform full economic analyses on the 10 therapies evaluated in this report, nor would the time needed to develop full ICER Reports (at least eight months) provide information in a useful timeframe for the public and policymakers. Therefore, this UPI Report is not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit price benchmark. Instead, the analyses focused on whether substantial new evidence existed that *could* justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases, we hope to take an important first step in

providing the public and policymakers with information they can use to advance the public debate on drug price increases.

ICER also received public input from state policymakers asking us to review price increases for insulin. We have added a section to this year's UPI Report looking at wholesale acquisition cost (WAC) price changes and net price changes for the top 10 (by revenue) insulin products in the United States (US).

2. Selection of Drugs to Review

The ultimate goal of the drug selection process was to identify the top 10 drugs whose estimated net price increases over a one-year period would have caused the greatest increase in drug spending in the US. Up to three additional drugs could be selected based on nominations received from the public. A detailed description of the entire UPI Protocol is available separately.

ICER obtained a list of the 100 drugs with the largest net sales revenue in the US in 2019. This information came from SSR Health, LLC, the health care division of SSR, LLC, an independent investment research firm. For each drug, we then determined the average WAC price changes over a one-year period. For this second UPI Report, we looked at the average price in 2019 compared with the average price in 2018.

Table 2.1. List of Top 100 Drugs with the Highest Net Sales Revenue (in Millions) in the US in 2019

Drug Name	2019 Net Sales Revenue	Four Quarter WAC % Change	Drug Name	2019 Net Sales Revenue	Four Quarter WAC % Change	Drug Name	2019 Net Sales Revenue	Four Quarter WAC % Change
Humira	14,864	6.2%	Lucentis	1,848	0.0%	Sprycel	1,191	6.0%
Revlimid	7,312	6.2%	Gardasil/9	1,831	7.5%	Odefsey	1,180	3.9%
Keytruda	6,305	2.4%	Pomalyst	1,795	6.2%	Simponi/Aria	1,159	5.9%
Enbrel	5,050	5.4%	Prolia	1,772	3.1%	Restasis	1,138	9.5%
Eliquis	4,755	6.0%	Xtandi	1,748	5.9%	Prezista/Prezcobix	1,119	6.8%
Eylea	4,644	0.0%	Botox	1,739	0.0%	Vimpat	1,097	7.0%
Rituxan	4,542	2.0%	Gilenya	1,736	4.3%	Descovy	1,078	3.9%
Stelara	4,346	6.7%	Januvia	1,724	5.1%	Tysabri	1,042	5.4%
Opdivo	4,344	2.6%	Jakafi	1,685	6.8%	Creon	1,041	6.2%
Biktarvy	4,225	3.9%	ProQuad/M-M-R II/Varivax	1,683	7.3%	Imfinzi	1,041	2.4%
Imbruvica	3,830	6.2%	Xyrem	1,643	--	Taltz	1,016	4.0%
Tecfidera	3,307	6.0%	Xeljanz	1,635	8.9%	Yervoy	1,004	2.6%
Ibrance	3,250	4.8%	Latuda	1,629	0.0%	Afinitor/Disperz	1,003	7.7%
Prevnar Family	3,209	4.5%	Humalog/Mix	1,615	0.0%	Velcade	1,001	0.0%
Trulicity	3,155	4.7%	Darzalex	1,567	4.7%	Copaxone	977	0.0%
Ocrevus	3,089	0.0%	Perjeta	1,546	2.8%	Hemlibra	957	0.0%
Remicade	3,079	0.0%	Aubagio	1,524	5.0%	Actemra	956	2.8%
Avastin	3,052	1.3%	Mavyret	1,473	0.0%	Acthar	953	0.0%
Genvoya	2,984	3.9%	Xgeva	1,457	3.0%	Spinraza	933	0.2%
Neulasta	2,814	0.0%	Otezla	1,457	5.0%	Entresto	925	9.6%
Herceptin	2,735	1.5%	Xifaxan	1,452	8.4%	Chantix	899	4.6%
Truvada	2,640	3.9%	Fluzone	1,452	--	Sandostatin/LAR	881	4.3%
Xarelto	2,313	6.8%	Ozempic	1,442	--	Humulin/Mix	880	0.0%
Cosentyx	2,220	9.5%	Jardiance	1,376	6.0%	Basaglar	876	0.0%
Vyvanse	2,174	2.3%	Novolog/Mix	1,330	2.5%	Epogen	867	0.0%
Orencia	2,146	6.0%	Lantus	1,296	6.7%	Rebif	867	6.2%
Victoza	2,140	10.0%	Activase/TNKase	1,293	0.1%	Vraylar	858	0.0%
Shingrix	2,136	3.0%	Tagrisso	1,268	1.0%	Abraxane	846	5.1%
Entyvio	2,120	6.4%	Tivicay	1,251	5.0%	Symbicort	829	5.5%
Invega Sustenna/Trinza	2,107	6.8%	Cimzia	1,234	7.0%	Tresiba	828	7.5%
Triumeq	2,062	3.0%	Alimta	1,220	3.7%	Orkambi	823	0.0%
Lyrica	2,012	4.7%	Avonex	1,202	2.0%	Esbriet	817	3.8%
Xolair	1,993	1.5%	Tecentriq	1,196	1.5%			
Dupixent	1,881	4.5%	Symdeko	1,192	0.0%			

No WAC change percentage is given when WAC data required to calculate WAC percentage change were not available in one or more quarters. Had the WAC percentage increases been larger than twice medical CPI, the drugs where WAC was unavailable still would not have been included in the list of drugs to be assessed.

We then determined which of those drugs had a WAC price increase over the one-year period that exceeded two times the rate of medical CPI. This was calculated as the difference between the average medical CPI using unadjusted rates, which was 2.83% for 2019 relative to 2018. The medical CPI is one of eight major components of the CPI recorded and reported by the US Bureau of Labor Statistics.[5] Medical CPI comprises medical care services (professional services, hospital and related services, and health insurance) and medical care commodities (medical drugs, equipment, and supplies).[6] Drugs whose WAC price percentage increases had not exceeded two times the rate of medical CPI (5.66%) were removed from further evaluation. Our intent in choosing the overall medical CPI and not its subcomponents was to reflect inflation in drug prices relative to inflation in the overall price of medical care.

Among those 33 drugs with a WAC price increase greater than twice the medical CPI, we determined *net* price changes over the one-year period. WAC and net price change per unit over the one-year period were adjusted for percentage change in price across different dosing strengths for any drug, if applicable, considering the relative sales volume of the various dosing strengths. Net price information was obtained from SSR Health.

We then ranked those drugs whose net price increases had the largest impact on US spending over the prior year. To create this ranking, we used calculations by SSR Health that dollarized the impact of net price changes year-on-year to give a representative rank ordering of the size of the impact by product during 2019, driven by both size of the product (in terms of total net sales) and size of the net price impact. Manufacturers were given the opportunity to correct these figures early in the process.

Table 2.2. Drugs with WAC Percentage Change Greater Than Twice Medical Care CPI

Drug Name	Increase in Spending Due to Net Price Change*	Drug Name	Increase in Spending Due to Net Price Change*
Invega Sustenna/Trinza	$203	Cimzia	-$101
Xifaxan	$173	Ozempic	-$128
Orencia	$145	Tresiba	-$170
Tecfidera	$118†	Xeljanz	-$201
Humira	$66	Jardiance	-$208
Entresto	$66	Eliquis	-$245
Vimpat	$58‡	Xarelto	-$411
Entyvio	$48§	Lantus	-$464
Rebif	$45	Victoza	-$485
Sprycel	$43	Imbruvica	**
Xtandi	$37#	Revlimid	**
Afinitor/Disperz	$36	Gardasil/9	**
Creon	$13	Pomalyst	**
Cosentyx	--¤	Jakafi	**
Stelara	-$17	ProQuad/ M-M-R II/ Varivax	**
Simponi/Aria	-$19	Prezista/Prezcobix	**
Restasis	-$34		

*In millions.

†Revised estimate based on information Biogen provided on net price increase and increase in spending for Tecfidera.

‡Revised estimate based on information UCB provided on net sales and net price increase for Vimpat.

§Revised estimate based on information Takeda provided on net price increase and increase in spending for Entyvio.

#Revised estimate based on information Astellas provided on net price increase and increase in spending for Xtandi that was provided beyond the deadline in the protocol.

¤Novartis provided information showing that the net price increase for Cosentyx was 0.0% over 2018-2019, which removed this drug from the assessment, per the protocol.

**Because of lack of face validity, we do not show the change in drug spending for drugs that had a net price higher than WAC price in at least one of the eight quarters in which data were captured.

Table 2.3 on the following page shows the 10 drugs that were chosen for assessment. The list began with ICER's assessment of the top 10 drugs based on estimated increase in drug spending due to increase in net price. After the cutoff date for informing ICER of corrections to net price, the manufacturer of secukinumab (Cosentyx®, Novartis) provided information showing that it did not have an increase in net price. The 2020 UPI Protocol did not anticipate this specific situation, but based on the 2019 UPI Protocol, secukinumab was removed from the review; it was too late to add a 10th drug. Also after the cutoff date, the manufacturer of enzalutamide (Xtandi®, Astellas) provided information showing that it would likely have been in position 11 on the list. The 2020 UPI Protocol did not anticipate this specific situation, but based on the 2019 UPI Protocol, enzalutamide

was kept in the review. This resulted in a total of nine drugs being assessed based on changes in price.

The UPI process allows for up to three additional drugs to be reviewed based on public input. We received feedback asking ICER to review etanercept (Enbrel®, Amgen) and it was added to the review. It was not included in the original top 10 drugs because its WAC price increase was slightly less than twice the medical CPI increase, however, the impact of its increase in net price on spending places it in the top position in terms of budget impact.

We did not add any other drugs, and so Table 2.3 includes nine drugs based on changes in drug spending and one drug based on public concern. The table also shows the percentage change in WAC, the percentage change in net price, and the increase in drug spending due to net price change from 2018 to 2019.

Table 2.3. Drugs Selected for Assessment

Drug	2018 to 2019 Percentage Change		Increase in Drug Spending Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Enbrel® (Etanercept)	5.4%	8.9%	$403
Invega Sustenna/Trinza® (Paliperidone Palmitate)	6.8%	10.7%	$203
Xifaxan® (Rifaximin)	8.4%	13.3%	$173
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Entyvio® (Vedolizumab)	6.4%	2.3%	$48
Xtandi® (Enzalutamide)	5.9%	2.5%†	$37†

*This is not a determination that the new evidence necessarily justified these price increases.
†Revised estimate based on information Astellas provided on net price increase and increase in spending for Xtandi that was provided beyond the deadline in the protocol.

3. Assessments

The goal of these assessments was to determine whether there was new clinical evidence in the prior year for the drugs under review. Based either on submissions from manufacturers or an ICER systematic review, ICER reviewed randomized controlled trials (RCTs), high quality comparative observational studies, and, for low frequency harms, large uncontrolled studies. For drugs with multiple indications, evidence was sought for indications responsible for at least 10% of a drug's utilization. ICER reviewed the quality of the new evidence using the widely accepted evidence grading system called GRADE.[4] For evidence that was felt to be high or moderate quality, ICER then assessed the magnitude of the additional net clinical benefit compared with what was previously known. Drugs under assessment without evidence meeting these criteria are reported as having price increases "unsupported by new clinical evidence." Drugs found to have moderate/high quality new evidence of a substantial improvement in net health benefit compared with what was previously believed are reported as having price increases "with new clinical evidence." A detailed description of the entire UPI Protocol is available separately.

3.1 Enbrel (Etanercept, Amgen)

Introduction

Enbrel (etanercept, Amgen) is a tumor necrosis factor (TNF) inhibitor.[7] It was approved by the Food and Drug Administration (FDA) in 1998, and it is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, plaque psoriasis (in patients ages four years or older), ankylosing spondylitis, and polyarticular juvenile idiopathic arthritis (in patients ages two years or older).[7]

Based on clinical input, the indications that account for greater than 10% of etanercept's use include:

- Rheumatoid arthritis
- Psoriatic arthritis
- Plaque psoriasis

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, etanercept's WAC increased by approximately 5.4%, while its net price increased by almost 9%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $403 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on etanercept as of January 2018. The manufacturer submitted 17 references (four conference presentations and 13 published manuscripts) to be considered as new clinical information, with 15 published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the 17 references, 12 of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.1 (Appendix A provides additional information on each study). Following the full-text review of the remaining five studies, one reference relating to one trial (SEAM-PsA) met our criteria of new moderate-to-high quality evidence on benefits and/or harms of etanercept. Additional information on the SEAM-PsA trial is provided below. The remaining four references presented previously known information about etanercept or were considered low-quality evidence (Table 3.2). We did not conduct an additional search for new clinical evidence.

Table 3.1. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Indication accounts for less than 10% of use	1
Intervention/comparison outside our scope	1
Outcomes not relevant to our scope	8
Study published outside of the timeframe of our review	2

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.2. Studies Not Meeting Criteria for New Moderate-to-High-Quality Evidence

Reasons	Number of References
Previously known information about etanercept efficacy	3
Low-quality evidence	1

Table 3.3. Summary of New Evidence

Baseline Evidence (Before January 2018)	New Evidence
Enbrel is indicated for the treatment of psoriatic arthritis. Prior to January 2018, several guidelines recommended conventional disease-modifying antirheumatic drugs (cDMARD) (e.g., methotrexate) as the drug of choice for treatment-naïve psoriatic arthritis patients. In 2018, the American College of Rheumatology (ACR)/National Psoriasis Foundation released a new guideline that recommended TNFs over a cDMARD in treatment-naïve patients. However, this recommendation was based on studies that involved different TNF therapies and were considered low-quality.[8-10]	The **SEAM-PsA trial** was the first RCT that evaluated the efficacy and safety of etanercept vs. methotrexate in treatment-naive psoriatic arthritis patients.[11] SEAM-PsA provides high-quality evidence on first-line use of etanercept compared with cDMARDs in treatment-naïve patients.

New Evidence

The **SEAM-PsA trial** (Mease 2019) was a randomized active-controlled trial conducted in patients with psoriatic arthritis who were biologic-naïve and had never received methotrexate treatment for psoriatic arthritis.[11] Patients who had received methotrexate treatment for psoriasis could enroll if they discontinued ≥6 months before study initiation and discontinuation had not been due to toxicity or intolerance. Patients were randomized 1:1:1 to either etanercept plus placebo weekly (etanercept monotherapy), oral methotrexate plus placebo weekly (methotrexate monotherapy), or etanercept plus oral methotrexate weekly (etanercept plus methotrexate). At 24 weeks of follow-up, there was significantly higher American College of Rheumatology (ACR) 20 response (60.9% vs. 50.7%, p=0.029), ACR50 response (44.4% vs. 30.6%, p=0.006), ACR70 response (29.2% vs. 13.8%, p<0.001), and minimal disease activity (MDA) response (35.9% vs. 22.9%, p=0.005) in the etanercept monotherapy arm compared to the methotrexate monotherapy arm. However, similar efficacy was observed between the etanercept and methotrexate monotherapy arms on the following outcomes: enthesitis score, dactylitis score, change in psoriasis-affected body surface area, and physical functioning assessed by Health Assessment Questionnaire Disability Index and the 36-Item Short-Form Health Survey. Outcomes were generally similar between the etanercept monotherapy and etanercept plus methotrexate arms.

Rating of Included Evidence (Quality and Magnitude)

The SEAM-PsA trial represents high-quality evidence assessing the clinical benefit of etanercept monotherapy versus methotrexate in treatment-naïve patients. Evidence from the SEAM-PsA trial indicates that etanercept was superior to methotrexate on ACR and MDA outcomes. As indicated in the UPI Protocol, having found high-quality evidence, ICER then looks at whether this evidence shows substantial new net benefits compared with what was previously believed.

As noted above, the 2018 ACR guidelines already recommended treatment with a TNF inhibitor in preference to methotrexate prior to the SEAM-PsA trial. This recommendation was considered to have been based on low-quality evidence. The European League Against Rheumatism (EULAR) updated its recommendations for the management of psoriatic arthritis in 2019 (published in 2020).[12] This 2019 recommendation states:

> *This recommendation […] places the use of csDMARDs in the management of PsA as first-line DMARDs. The continuous prioritisation of csDMARDs reflects consensual expert opinion within the taskforce that favoured the benefit to risk balance of csDMARDs and in particular MTX over biologicals, as well as their lower cost. Data supporting the use of MTX in PsA are scarce and include only small or inconclusive clinical trials, as well as indirect evidence stemming from the TICOPA trial and evidence from observational studies. However, the SEAM-PsA study, which was part of the SLR and has meanwhile been published in full, revealed that MTX has similar efficacy in joint counts, skin involvement, enthesitis, dactylitis and physical function as*

etanercept or even etanercept plus MTX. Given this similarity of effectiveness, and the differences in costs, this study further supports the taskforce's decision to place MTX and other csDMARDs at the top of the therapeutic algorithm[.]

Based on the above, EULAR explicitly looked at SEAM-PsA and despite its results, continues to recommend methotrexate as preferred first-line therapy over etanercept. Thus, while we have conflicting recommendations from ACR and EULAR, neither recommending body changed its recommendation based on SEAM-PsA. We must conclude that neither of these major organizations that make recommendations for the management of psoriatic arthritis changed its estimation of the balance of net benefits of etanercept versus methotrexate in a substantial way based on this clinical trial. That said, the manufacturer-supported SEAM-PsA trial is clearly the best trial to date looking at this question, providing high-quality evidence to caregivers and patients and informing those producing guidelines. The discussion above should make it clear that this is a close call.

Conclusion

After careful review of the evidence submitted by the manufacturer, we conclude that etanercept (Enbrel) had a price increase *unsupported* by new clinical evidence.

3.2 Invega Sustenna/Trinza (Paliperidone Palmitate, Janssen)

Introduction

Invega Sustenna (paliperidone palmitate) and Invega Trinza (paliperidone palmitate) are long-acting injectable preparations (of the same antipsychotic medication) that were first approved by the FDA in 2006.[13,14] Invega Sustenna is a one-month extended-release injection approved in adults to treat schizophrenia, schizoaffective disorder, and is used as an adjunct to mood stabilizers or antidepressants.[13] Invega Trinza is a three-month injection specifically indicated for the treatment of schizophrenia after patients have been adequately treated with Invega Sustenna for at least four months.[14] Based on clinical input, each individual indication accounts for greater than 10% of use.

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, the WAC for paliperidone palmitate across both its extended-release injectable forms increased by approximately 6.8%, while its net price increased by 10.7%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $203 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on paliperidone palmitate as of January 2018. The manufacturer did not submit any information to be considered for our review. We conducted an independent systematic literature review to look for new information from RCTs over the 24 months review timeframe (January 1, 2018 to December 31, 2019) on benefits and harms of paliperidone palmitate. The search was limited to English language studies of human subjects. The search strategies included a combination of indexing terms as well as free-text terms and are presented in Appendix Table B1. After the literature search and removal of duplicate citations, references went through two levels of screening at both the abstract and full-text levels by two reviewers.

Our literature search identified 44 potentially relevant references, of which eight full texts were reviewed. Of the eight references, two of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.4 (Appendix B provides more information on each study). Following the full-text review of the remaining six studies, none of them met our criteria of new high-quality evidence on the benefits and/or harms of paliperidone palmitate (Table 3.5). All six trials presented previously known information about paliperidone palmitate. The PRISMA flowchart is provided in Appendix Figure B1.

Table 3.4. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Study population outside approved label indication	1
Outcomes not relevant to our scope	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.5. Studies Not Meeting Criteria for New Moderate-to-High Quality Evidence

Reasons	Number of References
Previously known information about paliperidone ER related to efficacy	4
Previously known information about paliperidone ER related to safety	2

Conclusion

After careful review of the evidence, we conclude that paliperidone palmitate (Invega Sustenna, Invega Trinza) had a price increase *unsupported* by new clinical evidence.

3.3 Xifaxan (Rifaximin, Bausch Health)

Introduction

Xifaxan (rifaximin, Bausch Health) is a rifamycin antibacterial drug originally approved by the FDA in 2004.[15] It is indicated for the treatment of traveler's diarrhea (TD) caused by noninvasive strains of *Escherichia coli* (E. coli) in adult and pediatric patients (age 12 years and older), reduction in risk of overt hepatic encephalopathy recurrence in adults, and was most recently approved in 2015 for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.[15]

Based on the information provided by the manufacturer, the indications that account for greater than 10% of rifaximin's use include:

- Reduction in risk of overt hepatic encephalopathy recurrence
- Treatment of IBS-D

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, rifaximin's WAC increased by approximately 8.4%, while its net price increased by 13.3%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $173 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on rifaximin as of January 2018.[15] The manufacturer submitted 13 references (three conference presentations and 10 published manuscripts) to be considered as new clinical information, with five published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the 13 references, nine of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.6 (Appendix C provides additional information on each study). Following the full-text review of the remaining four studies, none of them met our criteria of new high-quality evidence on the benefits and/or harms of rifaximin (Table 3.7). All four trials presented previously known information about rifaximin. As an example, one of these trials that presented previously known information about rifaximin (Neff 2018) is highlighted below. We did not conduct an additional search for new clinical evidence.

Table 3.6. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Study published outside of the timeframe of our review	8
Outcomes not relevant to scope	1

For simplicity, we provide a single reason for excluding each study, although there may be multiple reasons why a study was excluded.

Table 3.7. Studies Not Meeting Criteria for New Moderate-to-High Quality Evidence

Reasons	Number of References
Previously known information about rifaximin for assessing efficacy	2
Previously known information about rifaximin related to safety	2

Study Not Meeting Criteria for New Moderate-to-High Quality Evidence

Neff 2018 is a systematic review reporting on the economic burden of hepatic encephalopathy and cost benefits of rifaximin, lactulose, and rifaximin plus lactulose for the management of hepatic encephalopathy.[16] In total, 16 references were identified through a PubMed search. The authors found that hepatic encephalopathy-related costs ranged from $5,370 to $50,120 annually per patient. Rifaximin was found to be associated with reduced health care costs, reduced hepatic encephalopathy related hospitalization risk, and showed favorable incremental cost-effectiveness ratios compared with lactulose.

Reason(s) for not Meeting Criteria for New Moderate-to-High Quality Evidence: Neff 2018 was a systematic review (without meta-analysis) of studies published before 2017. It summarizes previously known information about rifaximin.

Conclusion

After careful review of the evidence submitted by the manufacturer, we conclude that rifaximin (Xifaxan) had a price increase *unsupported* by new clinical evidence.

3.4 Orencia (Abatacept, Bristol Myers Squibb)

Introduction

Orencia (abatacept, Bristol Myers Squibb) is a selective T-cell costimulation modulator.[17] It was approved by the FDA in 2005, and it is currently indicated for the treatment of adults with moderately-to-severely active rheumatoid arthritis, adults with active psoriatic arthritis, and patients ages two years and older with moderately-to-severely active polyarticular juvenile idiopathic arthritis.[17]

Based on clinical input, the indications that account for greater than 10% of abatacept's use include:

- Adults with moderately-to-severely active rheumatoid arthritis
- Adults with active psoriatic arthritis

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, abatacept's WAC increased by 6%, while its net price increased by approximately 7.4%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $145 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on abatacept as of January 2018. The manufacturer submitted 59 references (29 conference presentations and 30 published manuscripts) to be considered as new clinical information, with 37 published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the 59 references, 39 of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.8 (Appendix D provides additional information on each study). Following the full-text review of the remaining 20 studies, none of them met our criteria of new high-quality evidence on the benefits and/or harms of abatacept (Table 3.9). Sixteen of these trials presented previously known information about abatacept, while the remaining four studies were considered low quality. Two of these low-quality trials (Suisse 2019 and Rigby 2019) are highlighted as examples below. We did not conduct an additional search for new clinical evidence.

Table 3.8. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Indication accounts for less than 10% of use	7
Intervention/comparison not relevant to scope	2
Study published outside of the timeframe of our review	22
Outcomes not relevant to scope	8

For simplicity, we provide a single reason for excluding each study, although there may be multiple reasons why a study was excluded.

Table 3.9. Studies Not Meeting Criteria for New Moderate-to-High Quality Evidence

Reasons	Number of References
Previously known information about abatacept related to efficacy	9
Previously known information about abatacept related to safety	6
Low-quality evidence	5

Studies Not Meeting Criteria for New High-Quality Evidence

Suissa 2019 used data from US-based MarketScan databases from 2007 to 2014 to evaluate the risk of adverse respiratory events associated with abatacept, compared with other biologic DMARDs (bDMARD), among patients with rheumatoid arthritis and chronic obstructive pulmonary disease (COPD).[18] Patients initiating abatacept (n=1,807) were matched on time-conditional propensity scores to patients initiating other bDMARDs (n=3,547). There was no significant difference in the adjusted hazard ratio (HR) of the combined endpoint of hospitalized COPD exacerbation, bronchitis, and hospitalized pneumonia or influenza with abatacept compared to other bDMARDs (HR: 0.87, 95% confidence interval [CI]: 0.68-1.12). A similar trend was observed for hospitalized exacerbation (HR: 0.60, 95% CI: 0.32-1.11), bronchitis (HR: 0.80, 95% CI: 0.56-1.14), hospitalized pneumonia/influenza (HR: 1.39, 95% CI: 0.91-2.13), and outpatient pneumonia/influenza (HR: 1.05, 95% CI: 0.86-1.29).

Reason(s) for Not Meeting Criteria for New High-Quality Evidence: Suissa 2019 is a well-performed observational study conducted to address the label warning for patients with rheumatoid arthritis and COPD patients based on a placebo-controlled trial.[18] It does not provide evidence specific to the label, however, as the concern was for COPD versus placebo, not versus other active therapies. And potentially more importantly, given the warning, it is likely that patients with COPD who are treated with abatacept are systematically different from those with COPD treated with another therapy, and the expectation would be that they are at a lower risk. As such, there would necessarily be concern about unmeasured confounding in an observational study even when propensity matching is used. We conclude that, using GRADE criteria, we have low-quality evidence for assessing a change in conclusions about net harms with abatacept. Under the UPI Protocol, we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence.

Rigby 2019 (conference poster) is a randomized single-blinded exploratory trial of abatacept versus adalimumab conducted in patients with early, active, moderate-to-severe rheumatoid arthritis who were biologic-naive. Patients were randomized 1:1 to receive either 125 mg abatacept weekly (n=40) or 40 mg adalimumab biweekly (n=40) for 24 weeks; all patients received a 25-40 mg dose of methotrexate weekly. At 24 weeks of follow-up, there was no significant difference between abatacept and adalimumab. A subgroup analysis was conducted by shared epitome status (SE +/-). In the SE+ subgroup, significantly more patients achieved ACR20 response (estimated difference: 29%; 95% CI: 5% to 52%), ACR50 response (estimated difference: 31%; 95% CI: 6% to 54%), ACR70 response (estimated difference: 28%; 95%CI: 2% to 46%), and Disease Activity Score-28 response (estimated difference: 27%; 95% CI: 1% to 46%) with abatacept (n=30) compared to adalimumab (n=31). There was no significant difference between abatacept (n=9) and adalimumab (n=9) in the SE- patients on all efficacy outcomes (actual data and 95% CI not reported). The interaction effect was not reported.

Reason(s) for Not Meeting Criteria for New High-Quality Evidence: Rigby 2019 explored the relationship between the clinical efficacy of abatacept and the SE status in patients with moderate-to-severe rheumatoid arthritis and showed a differential benefit of abatacept versus adalimumab in the SE+ patients. However, using GRADE criteria, Rigby 2019 was considered to provide low-quality evidence due to the limitations in the design of the study (e.g., lack of proper blinding, selective outcome reporting), imprecision of results (as shown by the wide CIs), and multiple testing.

Conclusion

After a careful review of the evidence, we conclude that Orencia (abatacept) had a price increase *unsupported* by new clinical evidence.

3.5 Tecfidera (Dimethyl Fumarate, Biogen)

Introduction

Tecfidera (dimethyl fumarate, Biogen) was approved by the FDA in March 2013 as an oral disease-modifying agent for relapsing forms of multiple sclerosis.[19]

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, dimethyl fumarate's WAC increased by 6%, while its net price increased by approximately 3.7%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $118 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on dimethyl fumarate as of January 2018. The manufacturer submitted 44 references (21 conference presentations and 23 published manuscripts) to be considered as new clinical information, with 17 published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the 44 references, 28 of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.10 (Appendix E provides additional information on each study). Following the full-text review of the remaining 16 studies, none met our criteria of new high-quality evidence on the benefits and/or harms of dimethyl fumarate (Table 3.11). Fifteen of these trials presented previously known information about dimethyl fumarate, while one study was considered low quality. As an example, one of the submitted trials that presented previously known information about dimethyl fumarate (Prosperini 2018) is highlighted below. We did not conduct an additional search for new clinical evidence.

Table 3.10. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Study published outside of the timeframe of our review	27
Study population outside approved label indication	1

For simplicity, we provide a single reason for excluding each study, although there may be multiple reasons why a study was excluded.

Table 3.11. Studies Not Meeting Criteria for New Moderate-to-High Quality Evidence

Reasons	Number of References
Previously known information about dimethyl fumarate related to efficacy	13
Previously known information about dimethyl fumarate related to safety	2
Low-quality evidence	1

Study Not Meeting Criteria for New Moderate-to-High Quality Evidence

Prosperini 2018 was a retrospective, propensity-score matching analysis of patients with relapsing-remitting multiple sclerosis that compared treatment with dimethyl fumarate (n=275) to fingolimod (n=275) in patients who were treatment-naïve, treatment switchers, or a composite of both.[20] The primary outcome of interest was the proportion of patients who achieved No Evident Disease Activity-3 (NEDA-3) status, a composite of the absence of disability worsening, clinical relapses, and radiologic activity, with the individual measures serving as secondary outcomes. In treatment-naïve patients, there was no significant difference between fingolimod and dimethyl fumarate on NEDA-3 (HR: 1.15, 95% CI: 0.59-2.52), no relapse (HR: 1.11, 95% CI: 0.40-3.05), no disability worsening (HR: 0.74, 95% CI: 0.19-2.95), or no radiologic activity (HR: 1.07, 95% CI: 0.52-2.19). For treatment switchers, while there was no significant difference between fingolimod and dimethyl fumarate for no radiologic activity (HR: 0.75, 95% CI: 0.46-1.21), fingolimod had significantly better rates of NEDA-3 (HR: 0.57, 95% CI: 0.38-0.86), no relapse (HR: 0.52, 95% CI: 0.29-0.93), and no disability worsening (HR: 0.33, 95% CI: 0.13-0.80).

Reason(s) for Not Meeting Criteria for New High-Quality Evidence: This study is consistent with what was previously known about dimethyl fumarate, with several prior real-world studies published before January 1, 2018 presenting consistent findings of similar effectiveness of dimethyl fumarate and fingolimod.[21-24]

Conclusion

After careful review of the evidence submitted by the manufacturer, we conclude that dimethyl fumarate (Tecfidera) had a price increase *unsupported* by new clinical evidence.

3.6 Humira (Adalimumab, AbbVie)

Introduction

Humira (adalimumab, AbbVie) is a humanized monoclonal antibody that binds specifically to TNF.[29] It was approved by the FDA in 2002, and it is indicated for the treatment of 10 different chronic diseases: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, adult and pediatric Crohn's disease, ulcerative colitis, plaque psoriasis, adult and adolescent hidradenitis suppurativa, and adult and pediatric noninfectious uveitis.[29]

Based on clinical input, the indications that account for greater than 10% of adalimumab's use include:

- Rheumatoid arthritis
- Psoriatic arthritis
- Adult Crohn's disease
- Ulcerative colitis
- Plaque psoriasis

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, adalimumab's WAC increased by approximately 6.2%, while its net price increased by 2%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $66 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on adalimumab as of January 2018. The manufacturer submitted 58 references (20 conference presentations and 38 published manuscripts) to be considered as new clinical information, with 54 published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the 58 references, 33 of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.12 (Appendix F provides additional information on each study). Following the full-text review of the remaining 25 studies, none of them met our criteria of new high-quality evidence on the benefits and/or harms of adalimumab (Table 3.13). Twenty of these trials presented previously known information about adalimumab, while the remaining five studies were considered low quality. As an example, one of the submitted trials that did not meet the UPI review criteria (Colombel 2018) is highlighted below. We did not conduct an additional search for new clinical evidence.

Table 3.12. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Study published outside of the timeframe of our review	4
Indication accounts for less than 10% of use	9
Intervention/comparison not relevant to our scope	10
Outcomes not relevant to our scope	9
Study protocol	1

For simplicity, we provide a single reason for excluding each study, although there may be multiple reasons why a study was excluded.

Table 3.13. Studies Not Meeting Criteria for New Moderate-to-High Quality Evidence

Reasons	Number of References
Previously known information about adalimumab related to efficacy	16
Previously known information about adalimumab related to safety	4
Low-quality evidence	5

Study Not Meeting UPI Review Criteria

Colombel 2018 was an open-label, randomized trial that compared tight control (escalating treatment based on clinical symptoms and biomarkers of inflammation) versus clinical management (escalating treatment based on clinical symptoms alone) in patients with moderate-to-severe Crohn's disease.[30] After nine weeks of baseline therapy of prednisone, patients were randomly assigned 1:1 to the tight control (n=122) or clinical management (n=122) group. Randomization was stratified by smoking status (yes or no), patient weight (<70 kg or ≥70 kg), and disease duration (≤2 years or >2 years). Open-label treatment was escalated in a stepwise manner every 12 weeks for all randomized patients, starting with adalimumab induction, to adalimumab maintenance therapy every other week, to adalimumab every week, and finally, a combination of daily azathioprine and weekly adalimumab. At 48 weeks, a significantly higher percentage of patients in the tight control group (46%) achieved the primary endpoint of mucosal healing defined by a Crohn's Disease Endoscopic Index of Severity score of less than four compared to the clinical management group (30%) with a Cochran-Mantel-Haenszel test adjusted risk difference of 16.1% (95% CI: 3.9-28.3).

Reason(s) for Not Meeting UPI Review Criteria: This study evaluated the benefit of tight control versus clinical management of Crohn's disease, with adalimumab in both comparison arms. It provides evidence on how best to use adalimumab but does not provide evidence for a new net benefit of adalimumab.

Conclusion

After careful review of the evidence submitted by the manufacturer, we conclude that adalimumab (Humira) had a price increase *unsupported* by new clinical evidence.

3.7 Entresto (Sacubitril/Valsartan, Novartis)

Introduction

Entresto (sacubitril/valsartan, Novartis) is a twice-daily, single-tablet regimen that combines sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin II receptor blocker).[31] It was approved by the FDA in 2015 and is currently indicated to reduce the risk of cardiovascular death and hospitalization in patients with reduced ejection fraction and chronic heart failure classified as New York Heart Association Class II-IV. Sacubitril/valsartan is also approved for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients (age one year and older).[31] Based on information provided by the manufacturer, only the first indication accounts for greater than 10% of use.

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, sacubitril/valsartan's WAC increased by approximately 9.6%, while its net price increased by 8%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $66 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on sacubitril/valsartan as of January 2018. The manufacturer submitted 18 references (four conference presentations and 14 published manuscripts) to be considered as new clinical information, with 11 published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the 18 references, nine of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.14 (Appendix G provides additional information on each study). Following the full-text review of the remaining nine references, three references (Velazquez 2019, Morrow 2019, and Ambrosy 2019) related to one RCT (PIONEER-HF) met our criteria of new high-quality evidence on the benefits and/or harms of sacubitril/valsartan. Additional information on the PIONEER-HF trial is provided below. The remaining six references presented previously known information about sacubitril/valsartan, provided new evidence of no clinical improvement with sacubitril/valsartan, or were considered low-quality evidence (Table 3.15). We did not conduct an additional search for new clinical evidence.

Table 3.14. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Study published outside of the timeframe of our review	7
Editorial	1
Conference citation – abstract/full presentation not provided	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.15. Studies Not Meeting Criteria for New Moderate-to-High Quality Evidence

Reasons	Number of References
New evidence of no clinical improvement with sacubitril/valsartan	1
Previously known information about sacubitril/valsartan related to efficacy	3
Low-quality evidence	2

Table 3.16. Summary of New Evidence

Baseline Evidence (Before January 2018)	New Evidence
Sacubitril/valsartan is used to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association Class II-IV) and reduced ejection fraction.[31] This indication was largely based on the PARADIGM-HD trial, which enrolled outpatients with stable chronic heart failure. The trial excluded hospitalized patients with acute decompensated heart failure as well as new-onset heart failure patients.	The **PIONEER-HF** trial was an RCT that evaluated the efficacy and safety of sacubitril/valsartan in patients with new-onset or worsening chronic heart failure who were stabilized following hospitalization for acute decompensated heart failure.[32,33,34] The PIONEER-HF trial extends the evidence base to populations that were excluded from previous trials – patients hospitalized for decompensated heart failure and patients with new heart failure.

New Evidence

The **PIONEER-HF trial** was a randomized, active-controlled trial conducted in patients hospitalized with acute decompensated heart failure with reduced ejection fraction.[33] Patients were randomized 1:1 to receive either sacubitril/valsartan (n=440) or enalapril (n=441) twice daily with medication initiation occurring in the hospital. The time-averaged reduction in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration was significantly greater for sacubitril/valsartan versus enalapril at four weeks (percent change: -46.7% vs. -25.3%; ratio of change: 0.71; 95% CI: 0.63-0.81) with significantly greater reductions occurring as early as week one and lasting through week eight.[33] At week eight of follow-up, the sacubitril/valsartan arm had significantly lower rates of rehospitalization for heart failure compared to the enalapril arm (41 vs. 64 events; rate ratio: 0.64; 95% CI: 0.42-0.97) as well as lower rates of the composite outcome of cardiovascular death or rehospitalization for heart failure (9.8% vs. 16.3%; HR: 0.58, 95% CI: 0.40-0.85).[32] Rates of all-cause death were numerically lower in the sacubitril/valsartan arm (2.3% vs. 3.4%; HR 0.66, 95% CI: 0.30-1.48).[32] Results from a pre-specified analysis showed that patients with

de novo heart failure had similar improvements in NT-proBNP concentration with sacubitril/valsartan versus enalapril (ratio of change: 0.65, 95% CI: 0.53-0.81) compared to patients with worsening chronic heart failure (ratio of change: 0.72, 95% CI: 0.63-0.83) at eight weeks.[34]

Rating of New Evidence (Quality and Magnitude)

The PIONEER-HF trial represents high quality evidence assessing the clinical benefit of sacubitril/valsartan in hospitalized patients with acute decompensated heart failure with reduced ejection fraction. Evidence from the PIONEER-HF trial indicates that sacubitril/valsartan reduced NT-proBNP concentration and the composite outcome of cardiovascular death or rehospitalization due to heart failure. This finding appears to be consistent irrespective of heart failure history (*de novo* vs. worsening or chronic heart failure). Although sacubitril/valsartan had previously demonstrated benefit in patients with stable heart failure with reduced ejection fraction, we believe there would have been potential concerns about its use in patients showing acute decompensation. As such, we believe that PIONEER-HF provides high-quality evidence of a substantial net benefit that was not previously known for patients with acute decompensated heart failure with reduced ejection fraction.

Conclusion

After careful review of the evidence, we conclude that sacubitril/valsartan (Entresto) had a price increase *with* new clinical evidence.

3.8 Vimpat (Lacosamide, UCB)

Introduction

Vimpat (lacosamide, UCB) is an antiepileptic drug first approved by the FDA in 2008. It is indicated for the treatment of partial-onset seizures in patients four years of age and older.[35] It is approved in the form of tablets, injections, and an oral solution. Lacosamide injection is indicated for the treatment of partial-onset seizures only in adult patients (≥17 years) as the safety of the injection has not yet been established in the pediatric population.[35]

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, lacosamide's WAC increased by 7%, while its net price increased by 5.6%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $58 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on lacosamide as of January 2018. The manufacturer submitted 25 references (19 conference presentations and six published manuscripts) to be considered as new clinical information, with eight published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the 25 references, 18 of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.17 (Appendix H provides more information on each study). Following the full-text review of the remaining seven studies, none met our criteria of new high-quality evidence on the benefits and/or harms of lacosamide (Table 3.18). All seven trials presented previously known information about lacosamide. As an example, one of the submitted trials that did not meet the UPI review criteria (Rosenow 2019) is highlighted below. We did not conduct an additional search for new clinical evidence.

Table 3.17. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Study published outside of the timeframe of our review	17
Intervention/comparison not relevant to scope	1

For simplicity, we provide a single reason for excluding each study, although there may be multiple reasons why a study was excluded.

Table 3.18. Studies Not Meeting Criteria for New Moderate-to-High Quality Evidence

Reasons	Number of References
Previously known information about lacosamide related to efficacy	4
Previously known information about lacosamide related to safety	3

Study Not Meeting UPI Review Criteria

Rosenow 2019[36] reports an interim analysis of a prospective observational study assessing patient preferences before a physician consultation for a new antiepileptic drug. The study utilized a discrete choice experiment survey that presented 12 choices between two hypothetical treatments defined by seven features, some of which included trouble thinking, developing clinical depression, and personality changes. In total, 127 patients across seven European countries, with a mean age of 47 years and a mean epilepsy duration of 13 years, were enrolled. At the time of the interim analysis, 37% of patients had discontinued more than two antiepileptic drugs, with the most common reasons being insufficient efficacy (42%) and adverse drug reactions (35.4%). Results showed that the two most important factors for weighing preferences for patients were the chance of becoming seizure-free and avoiding negative impact on cognition.

Reason(s) for Not Meeting UPI Review Criteria: This study was excluded because the intervention/comparison was not relevant to the scope of this review as it does not assess lacosamide specifically.

Conclusion

After careful review of the evidence submitted by the manufacturer, we conclude that lacosamide (Vimpat) had a price increase *unsupported* by new clinical evidence.

3.9 Entyvio (Vedolizumab, Takeda)

Introduction

Entyvio (vedolizumab) is a humanized monoclonal antibody that acts as an integrin receptor blocker.[25] The FDA approved vedolizumab in 2014 for the treatment of moderate-to-severe active ulcerative colitis as well as the treatment of moderate-to-severe active Crohn's disease. Based on clinical input, both indications account for greater than 10% of use.

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, vedolizumab's WAC increased by approximately 6.4%, while its net price increased by 2.3%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $48 million.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on vedolizumab as of January 2018. The manufacturer submitted 13 references (eight conference presentations and five published manuscripts) to be considered as new clinical information, with 12 published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the 13 references, two of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.19 (Appendix I provides additional information on each study). Following the full-text review of the remaining 11 references, one reference (Sands 2019) related to one RCT (VARSITY) met our criteria of new high-quality evidence on the benefits and/or harms of vedolizumab. Additional information on the VARSITY trial is provided below. The remaining 10 references presented previously known information about vedolizumab or were considered low-quality evidence (Table 3.20). We did not conduct an additional search for new clinical evidence.

Table 3.19. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Intervention/comparison not relevant to our scope	1
Study published outside of the timeframe of our review	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.20. Studies Not Meeting Criteria for New Moderate-to-High Quality Evidence

Reasons	Number of References
Low-quality evidence	6
Previously known information about vedolizumab related to efficacy	1
Previously known information about vedolizumab related to safety	3

Table 3.21. Summary of New Evidence

Baseline Evidence (Before January 2018)	New Evidence
At baseline, vedolizumab was indicated for patients with moderate-to-severe active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a TNF inhibitor.[25] There was no RCT directly comparing vedolizumab to any of the TNF inhibitors (in fact, there was no head-to-head trial of any of the biologics in the ulcerative colitis disease space).	The **VARSITY trial** evaluated the efficacy and safety of vedolizumab vs. adalimumab in biologic-naïve and biologic-experienced patients with moderate-to-severe active ulcerative colitis.[26] Although not clearly stated in the label, this trial likely played a part in expanding the indication for vedolizumab to include all patients with moderate-to-severe active ulcerative colitis (FDA label change: March 2020).

New Evidence

The **VARSITY trial** was a Phase IIIb multinational RCT that evaluated the efficacy and safety of vedolizumab versus adalimumab in 769 patients with moderately-to-severely active ulcerative colitis.[26] The trial enrolled TNF-naïve patients primarily but allowed previous exposure to TNF inhibitors in up to 25% of patients. Patients were randomized 1:1 to either vedolizumab (n=385) or adalimumab (n=386). At 52 weeks of follow-up, a higher proportion of patients in the vedolizumab treatment group achieved clinical remission (31.3% vs. 22.5%; difference: 8.8 percentage points, 95% CI: 2.5 to 15.0; P=0.006) as well as endoscopic improvement (39.7% vs. 27.7%; difference: 11.9 percentage points, 95% CI: 5.3 to 18.5; P<0.001) compared to the adalimumab group. Vedolizumab was also superior to adalimumab on clinical remission and endoscopic improvement in the TNF-naïve and TNF-exposed patients. Vedolizumab had numerically lower rates of corticosteroid-free clinical remission compared to adalimumab; however, these results were not statistically significant. Lower exposure adjusted incidence rates of infections (23.4 events vs. 34.6 events per 100 patient-years) as well as serious infections (1.6 events vs. 2.2 events per 100 patient-years) were observed in the vedolizumab-treated group compared to the adalimumab-treated group.

Rating of New Evidence (Quality and Magnitude)

Evidence from the VARSITY trial showed substantial and statistically significant differences in clinical remission and endoscopic improvement in favor of vedolizumab compared with adalimumab. An editorial published along with the VARSITY trial raised a concern that the trial protocol did not allow for dose escalation in either arm, and such dose escalation is typically performed more with adalimumab.[27] This creates some concerns about indirectness of the results of VARSITY to the difference in net benefits in patients with moderately-to-severely active ulcerative colitis that might be seen in real-world use of the two agents. This potentially lowers the quality of the evidence for this comparison from high to moderate within the GRADE system.

Following VARSITY, vedolizumab's label was changed to allow for its use in all patients with moderately-to-severely active ulcerative colitis, removing the requirement for an initial trial of TNF inhibitors. Furthermore, based on evidence from the VARSITY trial, the American Gastroenterological Association practice guideline now recommends vedolizumab as a preferred agent over adalimumab as a first-line option for patients with no previous exposure to biologic agents.[28] As such, we believe VARSITY provides at least moderate-quality evidence of a substantial net benefit that was not previously known for biologic-naïve patients with moderately-to-severely active ulcerative colitis.

Conclusion

After careful review of the evidence, we conclude that vedolizumab (Entyvio) had a price increase *with* new clinical evidence.

3.10 Xtandi (Enzalutamide, Astellas Pharma)

Introduction

Xtandi (enzalutamide, Astellas Pharma) is a nonsteroidal antiandrogen used for the treatment of prostate cancer. It was first approved by the FDA in 2012 for the treatment of metastatic castration-resistant prostate cancer (CRPC).[37] It later received a broader approval for all CRPC (metastatic and non-metastatic).[37] Xtandi has been more recently approved for the treatment of patients with metastatic castration-sensitive prostate cancer (CSPC).[37] Based on clinical input, both indications (CRPC and metastatic CSPC) account for greater than 10% of use.

Price Increase

Over the 12-month (four quarters) period for which price changes were assessed, enzalutamide's WAC increased by approximately 5.9%, while its net price increased by 2.5%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $37 million.

Note that this revised estimate was based on updated information Astellas provided on net price increase and increase in spending for enzalutamide that was provided beyond the deadline in the protocol, resulting in its inclusion on this list despite the lower estimated drug spending increase.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on enzalutamide as of January 2018. The manufacturer submitted nine published manuscripts as new clinical information to be considered, with five published within our timeframe of review (between January 1, 2018 and December 31, 2019). Of the nine references, five of them did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.22 (Appendix J provides more information on each study). The remaining four references (Hussein 2018, Tombal 2019, Armstrong 2019, and Davis 2019) related to three trials (PROSPER, ARCHES, and ENZAMET) met our inclusion criteria of new information on the benefits and/or harms of enzalutamide within the indications stated above. Additional details on the trials are provided below. We did not conduct an additional search for new clinical evidence on enzalutamide.

Table 3.22. Studies Not Meeting UPI Review Criteria

Reasons	Number of References
Study published outside of the timeframe of our review	4
Outcomes not relevant to the scope of review	1

For simplicity, we provided a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.23. Summary of New Evidence

Baseline Evidence (Before January 2018)	Included Evidence
Enzalutamide was approved for patients with metastatic CRPC based on data from three RCTs.[37]	The **PROSPER trial** evaluated the efficacy and safety of enzalutamide in patients with non-metastatic CRPC.[38,39] This trial led to the broadening of enzalutamide's indication to include non-metastatic CRPC (FDA decision: July 13, 2018).
	The **ARCHES trial** evaluated the efficacy and safety of enzalutamide in patients with metastatic CSPC.[40] This study led to the approval of enzalutamide for patients with metastatic CSPC.
	The **ENZAMET trial** evaluated the efficacy and safety of enzalutamide in patients with metastatic CSPC.[41] This study provides additional information on the clinical benefit of enzalutamide in metastatic CSPC, including its impact on overall survival.

New Evidence

The **PROSPER trial** was a Phase III multicentered RCT that evaluated the efficacy and safety of enzalutamide in patients with non-metastatic CRPC.[39] Patients were randomized 2:1 to receive either enzalutamide (n=933) or placebo (n=468); all patients continued to receive background androgen deprivation therapy (ADT). The trial reported a median metastasis-free survival of 36.6 months (95% CI 33.1 to NR) for the enzalutamide arm compared to 14.7 months (95% CI 14.2 to 15.0) for the placebo arm (HR: 0.29; 95% CI 0.24 to 0.35; p<0.0001). Time to the first use of a subsequent antineoplastic therapy and time to prostate-specific antigen (PSA) progression was longer with enzalutamide treatment than with placebo. The first interim analysis on overall survival (OS) showed 103 patients (11%) on enzalutamide had died compared with 62 (13%) in the placebo group. The median OS was not reached in either group. At the time of data cutoff, the HR for OS was 0.80 (95% CI 0.58 to 1.09; p=0.1519). Data from a secondary publication showed that patients who received enzalutamide had lower pain levels and prostate symptom burden and higher health-related quality of life.[38]

The **ARCHES trial** was a Phase III multicenter RCT that evaluated the efficacy and safety of enzalutamide in patients with metastatic CSPC.[40] Patients were randomized 1:1 to receive either enzalutamide once daily (n=574) or placebo once daily (n=576); all patients continued to receive background ADT. At the time of interim analysis, the median follow-up was 14.4 months. Enzalutamide demonstrated a statistically significant improvement in radiographic progression-free survival compared to placebo (enzalutamide median NR, placebo median: 19.0 months; HR: 0.39, 95% CI: 0.30-0.50). Interim analysis on OS showed 6.8% of patients in the enzalutamide group had died compared to 7.8% in the placebo group (HR: 0.81; 95% CI, 0.53 to 1.25). The median OS was not reached in either group.

The **ENZAMET trial** was a Phase III multicentered open-label RCT that evaluated the effects of early enzalutamide treatment on OS in patients with metastatic CSPC.[41] Patients were randomized 1:1 to receive either enzalutamide (n=563) or standard nonsteroidal antiandrogen therapy (standard-care group: bicalutamide, nilutamide, or flutamide) (n=562); all patients continued to receive background ADT. The median follow-up was 34 months. Enzalutamide demonstrated a statistically significant improvement in OS compared to the standard-care group (102 deaths vs. 143 deaths, HR: 0.67; 95% CI: 0.53 to 0.86). A statistically significant improvement in PSA progression-free survival (174 vs. 333 events, HR: 0.39; P<0.001) and in clinical progression-free survival (167 vs. 320 events, HR: 0.40; P<0.001) was also seen in enzalutamide compared with the standard-care group. However, treatment discontinuation due to adverse events was more frequent in the enzalutamide group than in the standard-care group (5.9% vs. 2.5%).

Rating of New Evidence (Quality and Magnitude)

Before these trials, enzalutamide was only used for the treatment of metastatic CRPC.

The PROSPER trial represents high-quality evidence assessing the benefit of enzalutamide in non-metastatic CRPC. Evidence from the PROSPER trial indicates that enzalutamide delays disease progression. Data on OS was preliminary and not yet mature; however, there was also a trend toward improved survival. ICER previously gave an evidence rating of "A" for treatment of non-metastatic CRPC with enzalutamide plus ADT versus ADT alone based primarily on the PROSPER trial. We again believe that PROSPER provides high-quality evidence of a substantial net benefit that was not previously known for patients with non-metastatic CRPC.

The ARCHES trial and the ENZAMET trial represent high-quality evidence assessing the benefit of enzalutamide in metastatic CSPC. Evidence from the ARCHES trial indicates that enzalutamide delays radiographic progression-free survival and showed a trend toward improvement in OS. In the ENZAMET trial, which had longer follow-up, enzalutamide substantially improved OS compared to an active comparator. These trials provide high-quality evidence of a substantial net benefit that was not previously known for patients with metastatic CSPC.

We conclude that the new evidence from the PROSPER trial, the ARCHES trial, and the ENZAMET trial provide high certainty of a substantial benefit for enzalutamide compared with what was previously known.

Conclusion

After careful review of the evidence, we conclude that enzalutamide (Xtandi) had a price increase *with* new clinical evidence.

4. Insulin

The discoverers of the initial process for isolating and purifying insulin, with a goal of keeping their process in the public domain, patented their work and sold that patent for $1 to the Board of Governors of the University of Toronto.[42] Yet insulin pricing has been a cause of ongoing concern in the US, with reports of rapid increases in insulin prices year over year,[43] much higher prices in the US than in other high-income countries,[44] and reports of severe financial toxicity harming patients and families.[45]

ICER received input from state policymakers suggesting that insulin be evaluated in the current UPI Report. We chose to include a review of insulins in this report while acknowledging that the UPI methodology, which focuses on net price increases, does not work well for medications like insulin for reasons including:

- Net prices paid by insurers for insulin have not seen recent increases despite increased out-of-pocket costs to patients due to escalating list prices[46]
- There are multiple manufacturers of insulin, so that even if one brand name version did have a significant increase in net price, the budget impact would be relatively small at the national level

Tables 4.1 and 4.2 on the following page show the results of our insulin review. Of note, the year-over-year change in WAC price looks at changes in WAC price for individual dosing formulations and so can be different from the change in average WAC price if sales of different dosing formulations differed between the years being compared. Changes in year-over-year net prices are similarly adjusted.

4.1. Pricing for Top 10 Insulin Products in the US (WAC)

Product	Manufacturer	2019 Sales (In Millions)	2018 Average WAC (Per Unit)	2019 Average WAC (Per Unit)	Year/Year WAC % Change
Humalog/Mix	Eli Lilly and Company	$1,669*	$33.64	$34.03	0.0%
Novolog/Mix	Novo Nordisk A/S	$1,330	$33.44	$34.35	2.5%
Lantus	Sanofi	$1,286†	$26.56	$28.34	5.2%†
Humulin/Mix	Eli Lilly and Company	$880	$48.48	$51.59	0.0%
Basaglar	Eli Lilly and Company	$876	$21.76	$21.76	0.0%
Tresiba	Novo Nordisk A/S	$828	$52.95	$55.63	7.5%
Levemir	Novo Nordisk A/S	$763	$28.68	$30.79	7.4%
Toujeo	Sanofi	$324†	$81.52	$86.30	4.4%†
Admelog	Sanofi	$263†	$27.48	$21.37	-44.1%
Novolin	Novo Nordisk A/S	$233	$13.77	$13.88	0.0%

WAC: wholesale acquisition cost

*Revised estimate based on information Eli Lilly provided on net sales for Humalog/Mix.

†Revised estimates based on information Sanofi provided on net sales and WAC increases for Lantus, Toujeo, and Admelog.

4.2. Pricing for Top 10 Insulin Products in the US (Net Price)

Product	Manufacturer	2018 Average Net Price (Per Unit)	2019 Average Net Price (Per Unit)	Year/Year Net Price % Change
Humalog/Mix*	Eli Lilly and Company	$7.82	$7.59	-3.0%
Novolog/Mix	Novo Nordisk A/S	$6.82	$5.48	-20.0%
Lantus†	Sanofi	$6.39	$4.71	-26.2%
Humulin/Mix*	Eli Lilly and Company	$26.91	$28.21	-1.0%
Basaglar*	Eli Lilly and Company	$7.39	$8.32	18.2%
Tresiba	Novo Nordisk A/S	$17.45	$14.18	-16.8%
Levemir	Novo Nordisk A/S	$7.11	$5.55	-21.8%
Toujeo†	Sanofi	$21.05	$16.79	-19.6%
Admelog†	Sanofi	$20.23	$12.26	-52.9%
Novolin	Novo Nordisk A/S	$4.43	$3.87	-11.7%

*Eli Lilly provided net pricing information based on price per vial rather than price per unit and could not verify the price per unit numbers above. We are showing Eli Lilly's numbers for year-over-year net price change.

†Sanofi was unable to verify net pricing information.

As shown in Table 4.1, in 2019, seven of the top 10 insulin products had sales of over $500 million, and all 10 had sales of over $200 million. From 2018 to 2019, list price (WAC) increased for five of these products, four had level pricing, and one had a decline in list price. Among the five products with increases in WAC, four experienced increases at more than medical CPI for the same period. However, as shown in Table 4.2, net price appears to have declined for nine of these products.

Thus, the actual price paid by the health system for these products was generally lower in 2019 than in 2018.

While higher net prices are the most potent force in driving up insurance premiums, and are thus important to plan sponsors, payers, and all members of a health system, list prices have important implications for patients. For uninsured patients who may experience the full cost of list pricing, insulin may be unaffordable. And high list prices can lead many insured patients to experience financial toxicity as well because health benefits often require payment of deductibles or co-insurance linked to the list price instead of the net price.

Overall, it appears that net prices for insulin generally declined between 2018 and 2019, while WAC generally stayed level or increased. The size of the WAC increases, when they occurred, were generally substantially greater than medical inflation overall and creates risk for greater financial toxicity for patients despite lower prices for payers.

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APPENDICES

Appendix A. Enbrel

Appendix Table A1. References Submitted by Amgen

Citation	Decision
Aquilani A, Marafon DP, Marasco E, et al. Predictors of Flare Following Etanercept Withdrawal in Patients with Rheumatoid Factor-negative Juvenile Idiopathic Arthritis Who Reached Remission while Taking Medication. J Rheumatol. 2018;45(7):956-961.	Indication accounts for less than 10% of use
Cohen S, Samad A, Karis E, et al. Decreased Injection Site Pain Associated with Phosphate-Free Etanercept Formulation in Rheumatoid Arthritis or Psoriatic Arthritis Patients: A Randomized Controlled Trial. Rheumatol Ther. 2019;6(2):245-254.	Intervention/comparison outside our scope
Bagel J, Samad AS, Stolshek BS, et al. Open-Label Study to Evaluate the Efficacy of Etanercept Treatment in Subjects With Moderate to Severe Plaque Psoriasis Who Have Failed Therapy With Apremilast. J Drugs Dermatol. 2018;17(10):1078-1082.	Low-quality evidence
Curtis JR, Trivedi M, Haraoui B, et al. Defining and characterizing sustained remission in patients with rheumatoid arthritis. Clin Rheumatol. 2018;37(4):885-893.	Outcomes not relevant to our scope
Khraishi M, Ivanovic J, Zhang Y, et al. Long-term etanercept retention patterns and factors associated with treatment discontinuation: a retrospective cohort study using Canadian claims-level data. Clin Rheumatol. 2018;37(9):2351-2360.	Outcomes not relevant to our scope
Gu T, Mutebi A, Stolshek BS, Tan H. Cost of biologic treatment persistence or switching in rheumatoid arthritis. Am J Manag Care. 2018;24(8 Spec No.):SP338-SP345.	Outcomes not relevant to our scope
Stolshek BS, Wade S, Mutebi A, De AP, Wade RL, Yeaw J. Two-year adherence and costs for biologic therapy for rheumatoid arthritis. Am J Manag Care. 2018;24(8 Spec No.):SP315-SP321.	Outcomes not relevant to our scope
Incerti D, Maksabedian EJ, Tkacz J, et al. Understanding the Impact of Dose Escalation on the Cost-Effectiveness of Etanercept Among Patients with Rheumatoid Arthritis. J Manag Care Spec Pharm. 2019 Mar; 25 (3A): S84-S85.	Outcomes not relevant to our scope
Gharaibeh M, Machaon B, McMorrow D, Maksabedian EJ, Stolshek BS. Effectiveness and Costs per Effectively Treated Patient with Targeted Immune Modulators for Rheumatoid Arthritis Using a Large US, Commercial Database. J Manag Care Spec Pharm. 2018 Oct; 24 (10A): S82.	Outcomes not relevant to our scope
Tkacz J, Maksabedian EJ, Incerti D, et al. Dose Escalation of Targeted Immune Modulators Among Patients with Rheumatoid Arthritis. J Manag Care Spec Pharm. 2018 Oct; 24 (10A): S82.	Outcomes not relevant to our scope
Tkacz J, Gharaibeh M, DeYoung KH, et al. Treatment Patterns and Costs in Biologic-Naïve Rheumatoid Arthritis Patients Initiating Etanercept or Adalimumab With or Without Methotrexate. J Manag Care Spec Pharm. 2018 Oct; 24 (10A): S81.	Outcomes not relevant to our scope
Behrens F, Meier L, Prinz JC, et al. Simultaneous Response in Several Domains in Patients with Psoriatic Disease Treated with Etanercept as Monotherapy or in Combination with Conventional Synthetic Disease-modifying Antirheumatic Drugs. J Rheumatol. 2018;45(6):802-810.	Previously known information about etanercept efficacy
Papp KA, Bourcier M, Poulin Y, et al. OBSERVE-5: Comparison of Etanercept-Treated Psoriasis Patients From Canada and the United States. J Cutan Med Surg. 2018;22(3):297-303.	Previously known information about etanercept efficacy

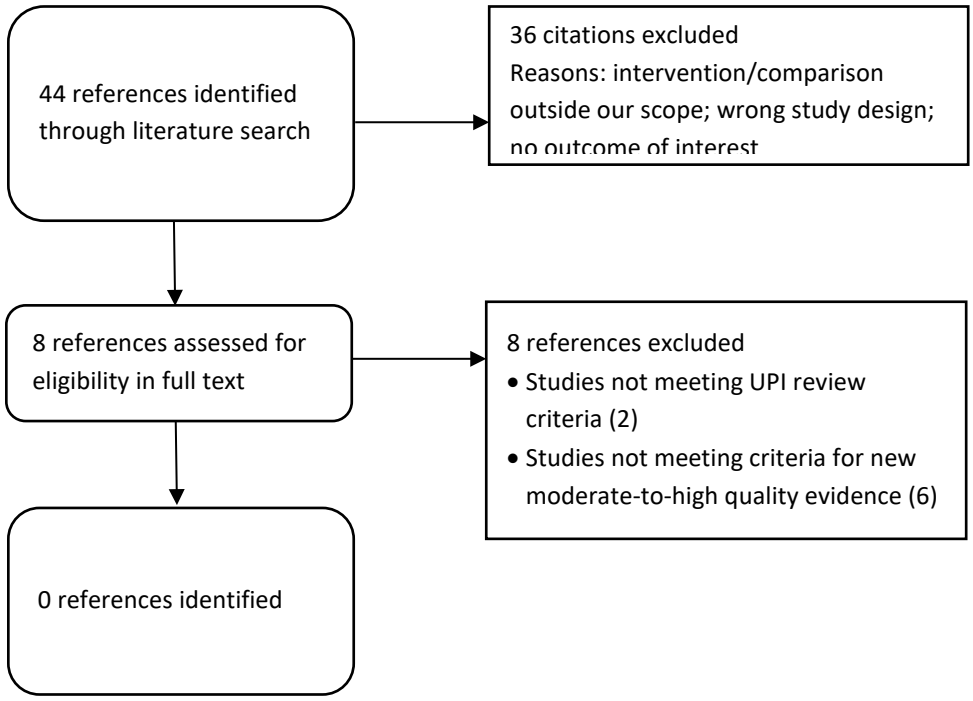
Citation	Decision
Smolen JS, Szumski A, Koenig AS, Jones TV, Marshall L. Predictors of remission with etanercept-methotrexate induction therapy and loss of remission with etanercept maintenance, reduction, or withdrawal in moderately active rheumatoid arthritis: results of the PRESERVE trial. Arthritis Res Ther. 2018;20(1):8.	Previously known information about etanercept efficacy
Tkacz J, Gharaibeh M, DeYoung KH, Wilson K, Collier D, Oko-Osi H. Treatment Patterns and Costs in Biologic DMARD-Naive Patients with Rheumatoid Arthritis Initiating Etanercept or Adalimumab with or Without Methotrexate. J Manag Care Spec Pharm. 2020;26(3):285-294.	Study published outside of the timeframe of our review
Gharaibeh M, Bonafede M, McMorrow D, Hernandez EJM, Stolshek BS. Effectiveness and Costs Among Rheumatoid Arthritis Patients Treated with Targeted Immunomodulators Using Real-World U.S. Data. J Manag Care Spec Pharm. 2020;26(8):1039-1049.	Study published outside of the timeframe of our review

Appendix B. Invega Sustenna/Trinza

Appendix Table B1. Search Strategy of Paliperidone Palmitate in EMBASE

#1	'paliperidone'/exp OR 'invega sustenna':ti,ab OR 'sustenna':ti,ab OR 'invega trinza':ti,ab OR 'Trinza':ti,ab OR 'paliperidone palmitate':ti,ab
#2	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp
#3	1 AND 2
#4	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#5	#3 NOT #4
#6	#5 and [English]/lim
#7	#6 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#8	#7 AND [2018-2019]/PY

Appendix Figure B1. PRISMA Flowchart Showing Results of Literature Search for Paliperidone Palmitate



Appendix Table B2. References Included in Full Text Screening

Citation	Decision
Chen YL, Chen KP, Chiu CC, Tai MH, Lung FW. Early predictors of poor treatment response in patients with schizophrenia treated with atypical antipsychotics. BMC Psychiatry. 2018 Dec 4;18(1):376.	Outcomes not relevant to our scope
Pu ZP, Li GR, Zou ZP, et al. A Randomized, 8-Week Study of the Effects of Extended-Release Paliperidone and Olanzapine on Heart Rate Variability in Patients With Schizophrenia. J Clin Psychopharmacol. 2019 May/Jun;39(3):243-248.	Previously known information about paliperidone related to safety
Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate 3-month versus 1-month formulation in patients with schizophrenia: comparison between European and non-European population. Neuropsychiatr Dis Treat. 2019 Feb 21;15:587-602.	Previously known information about paliperidone related to safety
Wu RQ, Lin CG, Zhang W, et al. Effects of Risperidone and Paliperidone on Brain-Derived Neurotrophic Factor and N400 in First-Episode Schizophrenia. Chin Med J (Engl). 2018 Oct 5;131(19):2297-2301.	Previously known information about paliperidone related to efficacy
Huang M, Yu L, Pan F, et al. A randomized, 13-week study assessing the efficacy and metabolic effects of paliperidone palmitate injection and olanzapine in first-episode schizophrenia patients. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Feb 2;81:122-130.	Previously known information about paliperidone related to efficacy
Fu DJ, Turkoz I, Walling D, et al. Paliperidone palmitate once-monthly maintains improvement in functioning domains of the Personal and Social Performance scale compared with placebo in subjects with schizoaffective disorder. Schizophr Res. 2018 Feb;192:185-193.	Previously known information about paliperidone related to efficacy
Alphs L, Bossie C, Mao L, et al. Treatment effect with paliperidone palmitate compared with oral antipsychotics in patients with recent-onset versus more chronic schizophrenia and a history of criminal justice system involvement. Early Interv Psychiatry. 2018 Feb;12(1):55-65.	Previously known information about paliperidone related to efficacy
Wang G, Ma L, Liu X, et al. Paliperidone Extended-Release Tablets for the Treatment of Methamphetamine Use Disorder in Chinese Patients After Acute Treatment: A Randomized, Double-Blind, Placebo-Controlled Exploratory Study. Front Psychiatry. 2019 Sep 19;10:656.	Study population outside approved label indication

Appendix C. Xifaxan

Appendix Table C1. References Submitted by Bausch Health

Citation	Decision
Rezaie A, Heimanson Z, McCallum R, Pimentel M. Lactulose Breath Testing as a Predictor of Response to Rifaximin in Patients With Irritable Bowel Syndrome With Diarrhea. Am J Gastroenterol. 2019;114(12):1886-1893.	Outcomes not relevant to scope
Oey RC, Buck LEM, Erler NS, et al. The efficacy and safety ofrifaximin-alpha: a 2-year observational study of overt hepatic encephalopathy. Therap Adv Gastroenterol. 2019;12:1756284819858256.	Previously known information about rifaximin for assessing efficacy
Neff G, Iii WZ. Systematic Review of the Economic Burden of Overt Hepatic Encephalopathy and Pharmacoeconomic Impact of Rifaximin. Pharmacoeconomics. 2018;36(7):809-822.	Previously known information about rifaximin for assessing efficacy
Lembo A, Heimanson Z, Cash BD. Characterization of abdominal pain response to rifaximin in patients with irritable bowel syndrome with diarrhea (IBS-D), by baseline pain severity [abstract #429]. Am J Gastroenterol. 2018;113(suppl):S252.	Previously known information about rifaximin related to safety
Lacy BE, Heimanson Z, Pimentel M. Rifaximin for improving abdominal pain and bloating symptoms in patients with irritable bowel syndrome with diarrhea (IBS-D) using modified definitions of pain response [abstract #453]. Am J Gastroenterol. 2018;113(suppl):S264.	Previously known information about rifaximin related to safety
Chautant F, Guillaume M, Robic MA, et al. Lessons from "real life experience" of rifaximin use in the management of recurrent hepatic encephalopathy. World J Hepatol. 2020;12(1):10-20.	Study published outside of the timeframe of our review
Tapper EB, Aberasturi D, Zhao Z, et al. Outcomes after hepatic encephalopathy in population-based cohorts of patients with cirrhosis. Aliment Pharmacol Ther. 2020;51(12):1397- 1405.	Study published outside of the timeframe of our review
Bozkaya D, Barrett AC, Migliaccio-Walle K. Cost-effectiveness of rifaximin treatment in patients with hepatic encephalopathy. Hepatology. 2014;60(4 Suppl):389A-390A.	Study published outside of the timeframe of our review
Jesudian AB, Ahmad M, Bozkaya D, Migliaccio-Walle K. Cost-effectiveness of rifaximin treatment in patients with hepatic encephalopathy. J Manag Care Spec Pharm. 2020;26(6):750-757.	Study published outside of the timeframe of our review
Lembo A, Rao SSC, Heimanson Z, Pimentel M. Abdominal Pain Response to Rifaximin in Patients With Irritable Bowel Syndrome With Diarrhea. Clinical and Translational Gastroenterology. 2020;11(3): e00144.	Study published outside of the timeframe of our review
Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology. 2016;151(6):1113-1121.	Study published outside of the timeframe of our review
Pimentel M, Cash BD, Lembo A, et al. Repeat rifaximin for irritable bowel syndrome: no clinically significant changes in stool microbial antibiotic sensitivity. Dig Dis Sci. 2017;62(9):2455-2463.	Study published outside of the timeframe of our review

Citation	Decision
Chey WD, Shah ED, DuPont HL. Mechanism of action and therapeutic benefit of rifaximin in patients with irritable bowel syndrome: a narrative review. Therap Adv Gastroenterol. 2020;13:1756284819897531.	Study published outside of the timeframe of our review

Appendix D. Orencia

Appendix Table D1. References Submitted by Bristol Myers Squibb

Citation	Decision
Brunner HI, Tzaribachev N, Vega-Cornejo G, et al. Subcutaneous Abatacept in Patients With Polyarticular-Course Juvenile Idiopathic Arthritis: Results From a Phase III Open-Label Study. Arthritis Rheumatol. 2018;70(7):1144-1154.	Indication accounts for less than 10% of use
Ruperto N, Brunner HI, Vega-Cornejo G, et al. Subcutaneous abatacept in patients aged 2– 17 years with juvenile idiopathic arthritis and inadequate response to biologic or non-biologic diseasemodifying antirheumatic drugs: results over 24 Months by juvenile idiopathic arthritis disease category [Poster presentation: 2378]. American College of Rheumatology and Association of Rheumatology Health Professionals (ACR/ARHP) Annual Scientific Meeting; October 19-24, 2018, Chicago, IL.	Indication accounts for less than 10% of use
Hara R, Umebayashi H, Takei S, et al. Intravenous abatacept in Japanese patients with polyarticular-course juvenile idiopathic arthritis: results from a phase III open-label study. Pediatr Rheumatol Online J. 2019;17(1):17.	Indication accounts for less than 10% of use
Ruperto N, Brunner H, Tzaribachev N, et al. Maintenance of clinical response in individual children with juvenile idiopathic arthritis treated with subcutaneous abatacept [Oral presentation: OP0056]. EULAR Annual European Congress of Rheumatology; June 12-15, 2019, Madrid, Spain.	Indication accounts for less than 10% of use
Ruperto N, Brunner H, Cornejo GV, et al. Growth and development in patients with polyarticular-course juvenile idiopathic arthritis treated with subcutaneous abatacept [Poster presentation: SAT0515]. EULAR Annual European Congress of Rheumatology; June 12–15, 2019, Madrid, Spain.	Indication accounts for less than 10% of use
Diener C, Horneff G. Comparison of adverse events of biologicals for treatment of juvenile idiopathic arthritis: a systematic review. Expert Opin Drug Saf. 2019;18(8):719-732.	Indication accounts for less than 10% of use
Klink AJ, Curtice TG, Gupta K, et al. Real-world outcomes among patients with early rapidly progressive rheumatoid arthritis. Am J Manag Care. 2019;25(10):e288-e295.	Indication accounts for less than 10% of use
An J, Bider-Canfield Z, Kang J, et al. Economic Evaluation of Anticyclic Citrullinated Peptide Positivity in Rheumatoid Arthritis. J Manag Care Spec Pharm. 2019;25(4):469-477.	Intervention/comparison not relevant to scope
Alemao E, Iannaccone CK, Weinblatt ME, Shadick NA. Association of Changes in Anticitrullinated Protein Antibody Levels With Resource Use and Disease Activity Measures in Rheumatoid Arthritis Patients a US Observational Cohort. Clin Ther. 2019;41(6):1057-1065.e3.	Intervention/comparison not relevant to scope
Suissa S, Hudson M, Dell'Aniello S, Shen S, Simon TA, Ernst P. Comparative safety of abatacept in rheumatoid arthritis with COPD: A real-world population-based observational study. Semin Arthritis Rheum. 2019;49(3):366-372.	Low-quality evidence

Citation	Decision
Rigby W, Buckner J, Bridges L, et al. The effect of HLA-DRB1 risk alleles on the clinical efficacy of abatacept and adalimumab in seropositive biologic-naïve patients with early, moderate-tosevere RA: data from a head-to-head single-blinded trial [Poster presentation: LB0008]. EULAR Annual European Congress of Rheumatology; June 12-15, 2019, Madrid, Spain.	Low-quality evidence
Chen YM, Huang WN, Liao TL, et al. Comparisons of hepatitis C viral replication in patients with rheumatoid arthritis receiving tocilizumab, abatacept and tofacitinib therapy. Ann Rheum Dis. 2019;78(6):849-850.	Low-quality evidence
Kurata I, Tsuboi H, Terasaki M, et al. Effect of Biological Disease-modifying Anti-rheumatic Drugs on Airway and Interstitial Lung Disease in Patients with Rheumatoid Arthritis. Intern Med. 2019;58(12):1703-1712.	Low-quality evidence
Shahabi A, Shafrin J, Zhao L, et al. The economic burden of switching targeted disease-modifying anti-rheumatic drugs among rheumatoid arthritis patients. J Med Econ. 2019;22(4):350-358.	Low-quality evidence
Emery P, Burmester GR, Bykerk VP, et al. Re-treatment with abatacept plus methotrexate for disease flare after complete treatment withdrawal in patients with early rheumatoid arthritis: 2-year results from the AVERT study. RMD Open. 2019;5(1):e000840.	Outcomes not relevant to our scope
Choquette D, Bessette L, Alemao E, et al. Persistence rates of abatacept and TNF inhibitors used as first or second biologic DMARDs in the treatment of rheumatoid arthritis: 9 years of experience from the Rhumadata® clinical database and registry. Arthritis Res Ther. 2019;21(1):138.	Outcomes not relevant to our scope
Ebina K, Hashimoto M, Yamamoto W, et al. Correction to: Drug tolerability and reasons for discontinuation of seven biologics in 4466 treatment courses of rheumatoid arthritis-the ANSWER cohort study. Arthritis Res Ther. 2019;21(1):114.	Outcomes not relevant to our scope
Ebina K, Hashimoto M, Yamamoto W, et al. Drug tolerability and reasons for discontinuation of seven biologics in 4466 treatment courses of rheumatoid arthritis-the ANSWER cohort study [published correction appears in Arthritis Res Ther. 2019 May 6;21(1):114]. Arthritis Res Ther. 2019;21(1):91.	Outcomes not relevant to our scope
Harrold LR, Litman HJ, Connolly SE, et al. Effect of Anticitrullinated Protein Antibody Status on Response to Abatacept or Antitumor Necrosis Factor-α Therapy in Patients with Rheumatoid Arthritis: A US National Observational Study. J Rheumatol. 2018;45(1):32-39.	Outcomes not relevant to our scope
Patel V, Pulungan Z, Shah A, et al. Comparison of infection-related hosp+A14italization risk and cost in TNFi-experienced medicare beneficiaries with rheumatoid arthritis treated with abatacept or other targeted disease-modifying anti-rheumatic drugs [Poster presentation: 1801]. American College of Rheumatology and The Association of Rheumatology Professionals (ACR/ARP) Annual Meeting; November 8-13, 2019, Atlanta, GA.	Outcomes not relevant to our scope
Foo J, Morel C, Bergman M, et al. Cost per response for abatacept versus adalimumab in patients with seropositive, erosive early rheumatoid arthritis in the US, Germany, Spain, and Canada. Rheumatol Int. 2019;39(9):1621-1630.	Outcomes not relevant to our scope

Citation	Decision
Shafrin J, Tebeka MG, Price K, Patel C, Michaud K. The Economic Burden of ACPA-Positive Status Among Patients with Rheumatoid Arthritis. J Manag Care Spec Pharm. 2018;24(1):4-11.	Outcomes not relevant to our scope
Harrold LR, Litman HJ, Connolly SE, et al. Comparative Effectiveness of Abatacept Versus Tumor Necrosis Factor Inhibitors in Patients with Rheumatoid Arthritis Who Are Anti-CCP Positive in the United States Corrona Registry. Rheumatol Ther. 2019;6(2):217-230.	Previously known information about abatacept related to efficacy
Ogawa N, Ohashi H, Ota Y, et al. Multicenter, observational clinical study of abatacept in Japanese patients with rheumatoid arthritis [published correction appears in Immunol Med. 2019 Jun 11;:1-3]. Immunol Med. 2019;42(1):29-38.	Previously known information about abatacept related to efficacy
Strand V, Alemao E, Lehman T, et al. Improved patient-reported outcomes in patients with psoriatic arthritis treated with abatacept: results from a phase 3 trial. Arthritis Res Ther. 2018;20(1):269.	Previously known information about abatacept related to efficacy
Bykerk VP, Burmester GR, Combe BG, et al. On-drug and drug-free remission by baseline symptom duration: abatacept with methotrexate in patients with early rheumatoid arthritis [published correction appears in Rheumatol Int. 2019 Feb 5;:]. Rheumatol Int. 2018;38(12):2225-2231.	Previously known information about abatacept related to efficacy
Jansen DTSL, Emery P, Smolen JS, et al. Conversion to seronegative status after abatacept treatment in patients with early and poor prognostic rheumatoid arthritis is associated with better radiographic outcomes and sustained remission: post hoc analysis of the AGREE study. RMD Open. 2018;4(1):e000564.	Previously known information about abatacept related to efficacy
Emery P, Tanaka Y, Bykerk VP, et al. Efficacy and Safety of Abatacept in Combination with MTX in Early, MTX-Naïve, Anti-Citrullinated Protein Antibody–Positive Patients with RA: Primary and 1-Year Results from a Phase IIIb Study [Poster presentation: 563]. American College of Rheumatology and Association of Rheumatology Health Professionals (ACR/ARHP) Annual Scientific Meeting; October 19-24, 2018, Chicago, IL.	Previously known information about abatacept related to efficacy
Emery P, Tanaka Y, Bykerk V, et al. Patient-reported outcomes of abatacept in combination with MTX in early, MTX-Naïve, ACPA positive patients with RA: 1-Year results from a phase IIIb study [Poster presentation: 1423]. American College of Rheumatology and The Association of Rheumatology Professionals (ACR/ARP) Annual Meeting; November 8-13, 2019, Atlanta, GA.	Previously known information about abatacept related to efficacy
Fleischmann R, Weinblatt M, Ahmad H, et al. Efficacy of Abatacept and Adalimumab in Patients with Early Rheumatoid Arthritis With Multiple Poor Prognostic Factors: Post Hoc Analysis of a Randomized Controlled Clinical Trial (AMPLE). Rheumatol Ther. 2019;6(4):559-571.	Previously known information about abatacept related to efficacy
Oryoji K, Yoshida K, Kashiwado Y, et al. Shared epitope positivity is related to efficacy of abatacept in rheumatoid arthritis. Ann Rheum Dis. 2018;77(8):1234-1236.	Previously known information about abatacept related to efficacy
Ozen G, Pedro S, Schumacher R, Simon TA, Michaud K. Safety of abatacept compared with other biologic and conventional synthetic disease-modifying	Previously known information about abatacept related to safety

Citation	Decision
antirheumatic drugs in patients with rheumatoid arthritis: data from an observational study. Arthritis Res Ther. 2019;21(1):141.	
Genovese MC, Pacheco-Tena C, Covarrubias A, et al. Longterm Safety and Efficacy of Subcutaneous Abatacept in Patients with Rheumatoid Arthritis: 5-year Results from a Phase IIIb Trial. J Rheumatol. 2018;45(8):1085-1092.	Previously known information about abatacept related to safety
Simon TA, Soule BP, Hochberg M, et al. Safety of Abatacept Versus Placebo in Rheumatoid Arthritis: Integrated Data Analysis of Nine Clinical Trials. ACR Open Rheumatol. 2019;1(4):251-257.	Previously known information about abatacept related to safety
Jin Y, Kang EH, Brill G, Desai RJ, Kim SC. Cardiovascular (CV) Risk after Initiation of Abatacept versus TNF Inhibitors in Rheumatoid Arthritis Patients with and without Baseline CV Disease. J Rheumatol. 2018;45(9):1240-1248.	Previously known information about abatacept related to safety
Kang EH, Jin Y, Brill G, et al. Comparative Cardiovascular Risk of Abatacept and Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis With and Without Diabetes Mellitus: A Multidatabase Cohort Study. J Am Heart Assoc. 2018;7(3):e007393.	Previously known information about abatacept related to safety
Paul D, Yermilov I, Gibbs S, et al. Real-world evaluation of persistence with early-line abatacept versus tumor necrosis factor-inhibitors for rheumatoid arthritis complicated by poor prognostic factors [Poster presentation: SAT0157]. EULAR Annual European Congress of Rheumatology; June 12-15, 2019, Madrid, Spain.	Previously known information about abatacept related to safety
Lamerato L, Price K, Szymialis R, et al. Comparative evaluation of treatment patterns and healthcare utilization of newly-diagnosed rheumatoid arthritis patients by anti-cyclic citrullinated peptide antibody status. J Med Econ. 2018;21(3):231-240.	Study published outside of the timeframe of our review
Pedro S, Mikuls T, Zhuo J, Michaud K. Hospitalization and mortality outcomes in rheumatoid arthritis patients with lung disease. Oral presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Zhuo J, Zhang S, Knapp K, et al. Examination of interstitial lung disease in patients with rheumatoid arthritis – prevalence, time to onset, and clinical characteristics. Oral presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Bergstra SA, Vega-Morales D, Murphy E, et al. BMI and treatment survival in RA patients starting treatment with TNFα-inhibitors: long term follow-up in the real life METEOR registry. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Emery P, Tanaka Y, Bykerk VP, et al. Maintenance of clinical response with abatacept in combination with MTX in individual patients with early RA who are MTX-naïve and anticitrullinated protein antibody (ACPA)+: results from the induction period of AVERT-2, a randomised phase IIIb study. Poster presented	Study published outside of the timeframe of our review

Citation	Decision
at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	
Emery P, Tanaka Y, Bykerk VP, et al. Maintenance of SDAI remission and patientreported outcomes (PROs) following dose deescalation of abatacept in MTX-naïve, anticitrullinated protein antibody (ACPA)+ patients with early RA: results from AVERT-2, a randomised phase IIIb study. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Gandhi Y, Connolly S, Huang G, Wong R, Chilewski S, Murthy B. The relationship between abatacept exposure and efficacy measures in early MTX-naive anti-citrullinated protein antibody-positive patients with RA during the deescalation period of a phase IIIb study. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Klink AJ, Han X, Lobo F, Szymialis A, Lam J, Feinberg B. Clinical benefits reported in AMPLE trial observed in a real-world (RW) cohort of US rheumatoid arthritis (RA) patients. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Pachai C, Connolly S, Landis J, et al. Impact of baseline erosion score on response to treatment and future radiological damage in AVERT-2, a randomised phase IIIb study of abatacept in MTX-naïve, anti-citrullinated protein antibody– positive (ACPA+) patients with early RA. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Pedro S, Mikuls T, Zhuo J, Michaud K. Discontinuation of DMARD use in rheumatoid arthritis patients with lung disease. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Rigby W, Buckner J, Louis Bridges Jr S, et al. The effect of HLA-DRB1 risk alleles on the clinical efficacy and safety of abatacept in seropositive, biologic-naive patients with early, moderate-to-severe RA treated with abatacept or adalimumab: data from the open-label switch period of the head-to-head single-blinded 'Early AMPLE' trial. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Suissa S, Brassard P, Dominique AL, Simon TA, Hudson M. Risk factors for serious infections in patients with RA initiating treatment with biologic DMARDs: a real-world population-based observational study. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Zhuo J, Bryson J, Xia Q, et al. Role of shared epitope on the effectiveness of TNFi treatment for patients with rheumatoid arthritis. Poster presented at:	Study published outside of the timeframe of our review

Citation	Decision
European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	
Zhuo J, Bryson J, Xia Q, et al. Role of shared epitope in the prognosis of rheumatoid arthritis in relation to ACPA positivity. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Han X, Yermilov I, Gibbs S, Broder M. Persistence with abatacept versus tumor necrosis factor inhibitors for rheumatoid arthritis complicated by positive anti-cyclic citrullinated peptide/rheumatoid factor or other poor prognostic factors [abstract]. Ann Rheum Dis. 2020;79(suppl 1):1445-46.	Study published outside of the timeframe of our review
Han X, Xia Q, Bao Y, et al. Pooled analysis of association between abatacept or other target disease-modifying anti-rheumatic drugs (tDMARD) and type 2 diabetes mellitus (T2DM)- related healthcare resource utilization (HCRU) and costs in TNFi-naïve rheumatoid arthritis (RA) patients with T2DM [abstract]. Ann Rheum Dis. 2020;79(suppl 1):19606.	Study published outside of the timeframe of our review
Park SH, Han X, Lobo F, Nanji S, Patel D. A cost per responder analysis of abatacept versus adalimumab for the treatment of rheumatoid arthritis among patients with shared epitope (SE) positivity from a United States payer perspective [abstract]. Ann Rheum Dis. 2020;79(suppl 1):1872-73.	Study published outside of the timeframe of our review
Suryavanshi M, Suri S, Bao Y, Ruiz M, Patel V, Madera-Miranda E. Patient characteristics, comorbidities, and infection outcomes among rheumatoid arthritis (RA) patients in Puerto Rico (PR) [abstract]. Ann Rheum Dis. 2020;79 (suppl 1):1426.	Study published outside of the timeframe of our review
Brunner H, Tzaribachev N, Louw I, et al. Maintenance of minimal disease activity or inactive disease status and patient-reported outcomes in individual paediatric patients with juvenile idiopathic arthritis treated with subcutaneous abatacept. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Mease PJ, Zhuo J, Weerasinghe R, Xia Q, Samal C, Sharma N. Patient characteristics, treatment patterns, and resource utilization of sjogren's syndrome patients in a large US health network. Poster presented at: European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology; June 3-6, 2020: Virtual Meeting.	Study published outside of the timeframe of our review
Han X, Zhuo J, Xia Q, et al. A real-world study of clinical outcomes with abatacept versus janus kinase inhibitors in patients with RA who are anti-citrullinated protein antibody and rheumatoid factor positive. Poster presentation at Congress of Clinical Rheumatology (CCR) West; October 8-11, 2020, San Diego, CA.	Study published outside of the timeframe of our review

Citation	Decision
Han X, Zhuo J, Xia Q, et al. Patient-reported outcomes of abatacept versus janus kinase inhibitor in rheumatoid arthritis patients with anti-citrullinated protein antibody and rheumatoid factor positivity. Poster presentation at Congress of Clinical Rheumatology (CCR) West; October 8-11, 2020, San Diego, CA.	Study published outside of the timeframe of our review

Appendix E. Tecfidera

Appendix Table E1. References Submitted by Biogen

Citation	Decision
Oshima Y, Tanimoto T, Yuji K, Tojo A. Drug-associated progressive multifocal leukoencephalopathy in multiple sclerosis patients. Mult Scler. 2019;25(8):1141-1149.	Low-quality evidence
Sloane J, Phillips T, Calkwood J, et al. Delayed-release dimethyl fumarate demonstrated no difference in clinical outcomes versus fingolimod in patients with relapsing-remitting multiple sclerosis: Results from the real-world EFFECT study. Presented at the 2018 AAN Annual Meeting, 21-27 April, 2018, Los Angeles, CA.	Previously known information about dimethyl fumarate related to efficacy
Braune S, Grimm S, van Hövell P, et al. Comparative effectiveness of delayed-release dimethyl fumarate versus interferon, glatiramer acetate, teriflunomide, or fingolimod: results from the German NeuroTransData registry. J Neurol. 2018; Dec (12): 2980–2992.	Previously known information about dimethyl fumarate related to efficacy
Buron MD, Chalmer TA, Sellebjerg F, et al. Comparative effectiveness of teriflunomide and dimethyl fumarate: A nationwide cohort study. Neurology. 2019;92(16):e1811-e1820.	Previously known information about dimethyl fumarate related to efficacy
Calkwood J, Cohan S, Chan A, et al. Real-world Effectiveness of Delayed-release Dimethyl Fumarate in Relapsing-remitting Multiple Sclerosis Patients Who Are Treatment-naïve or Treated With Only One Prior Therapy: Final Results from the EFFECT Study. Neurology. 2018 April; 90 (15 Supplement): 373.	Previously known information about dimethyl fumarate related to efficacy
Giles K, Balashov K, Jones CC, et al. Real-world Efficacy of Delayed-Release Dimethyl Fumarate in Early Multiple Sclerosis: Interim Results from ESTEEM. Mult Scler J. 2018; 24: 595.	Previously known information about dimethyl fumarate related to efficacy
Kresa-Reahl K, Repovic P, Robertson D, Okwuokenye M, Meltzer L, Mendoza JP. Effectiveness of Delayed-release Dimethyl Fumarate on Clinical and Patient-reported Outcomes in Patients With Relapsing Multiple Sclerosis Switching From Glatiramer Acetate: RESPOND, a Prospective Observational Study [published correction appears in Clin Ther. 2019 Jun 26;:]. Clin Ther. 2018;40(12):2077-2087.	Previously known information about dimethyl fumarate related to efficacy
Zipoli V, Tortorella P, Goretti B, et al. Effect of delayed-release dimethyl fumarate on cognition in Italian patients with relapsing remitting multiple sclerosis: the phase 4 StarTec study. Mult Scler J. 2018; 24: 198-199.	Previously known information about dimethyl fumarate related to efficacy
Giles K, Hanna J, Wu F, et al. Efficacy of Delayed-Release Dimethyl Fumarate in Newly Diagnosed and Other Early Multiple Sclerosis Patients, and Patients Switching from Interferon or Glatiramer Acetate, in Routine Medical Practice: Interim Results from ESTEEM. Neurology. 2018 April; 90 (15S): P1. 367.	Previously known information about dimethyl fumarate related to efficacy
Nicholas J, Boster A, Wu N, et al. Comparison of Disease-Modifying Therapies for the Management of Multiple Sclerosis: Analysis of Healthcare Resource Utilization and Relapse Rates from US Insurance Claims Data. Pharmacoecon Open. 2018;2(1):31-41.	Previously known information about dimethyl fumarate related to efficacy

Citation	Decision
Hersh C, Harris H, Cohn S, et al. Comparative effectiveness and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 36-month follow-up. Mult Scler J. 2018 October; 24: 266.	Previously known information about dimethyl fumarate related to efficacy
Vollmer B, Ontaneda D, Bandyopadhyay A, et al. Discontinuation and comparative effectiveness of dimethyl fumarate and fingolimod in 2 centers. Neurol Clin Pract. 2018;8(4):292-301.	Previously known information about dimethyl fumarate related to efficacy
Ontaneda D, Nicholas J, Carraro M, et al. Comparative effectiveness of dimethyl fumarate versus fingolimod and teriflunomide among MS patients switching from first-generation platform therapies in the US. Mult Scler Relat Disord. 2019;27:101-111.	Previously known information about dimethyl fumarate related to efficacy
Prosperini L, Lucchini M, Haggiag S, et al. Fingolimod vs dimethyl fumarate in multiple sclerosis: A real-world propensity score-matched study. Neurology. 2018;91(2):e153-e161.	Previously known information about dimethyl fumarate related to efficacy
Hellwig K, Rog D, McGuigan C, et al. An international registry tracking pregnancy outcomes in women treated with dimethyl fumarate. Poster (P1147) presented at ECTRIMS, 11-13 September, 2019, Stockholm, Sweden.	Previously known information about dimethyl fumarate related to safety
Pandey K, Giles K, Balashov K, et al. Safety and effectiveness of delayed-release dimethyl fumarate maintained over 4-years in multiple sclerosis patients treated in routine medical practice. Poster (P649) presented at ECTRIMS, 11-13 September, 2019, Stockholm, Sweden.	Previously known information about dimethyl fumarate related to safety
Alroughani R, Huppke P, Pultz J, et al. Long-term safety and efficacy of delayed-release dimethyl fumarate in pediatric patients with relapsing-remitting multiple sclerosis: A long-term extension of the FOCUS study. Poster (P375) presented at ECTRIMS, 11-13 September, 2019, Stockholm, Sweden.	Study population outside approved label indication
Chan A, Cutter G, Fox RJ, et al. Comparative effectiveness of delayed-release dimethyl fumarate versus glatiramer acetate in multiple sclerosis patients: results of a matching-adjusted indirect comparison. J Comp Eff Res. 2017 Jun;6(4):313-323.	Study published outside of the timeframe of our review
Fox RJ et al. Comparative effectiveness using a matching-adjusted indirect comparison between delayed-release dimethyl fumarate and fingolimod for the treatment of multiple sclerosis. Curr Med Res Opin. 2017;33:175-183.	Study published outside of the timeframe of our review
Kalincik T, Butzkueven H. Observational data: Understanding the real MS world. Mult Scler. 2016 Nov;22(13):1642-1648.	Study published outside of the timeframe of our review
Kalincik T, Spelman T, Jokubaitis V, et al. Effectiveness of fingolimod, dimethyl fumarate and teriflunomide in relapsing-remitting multiple sclerosis: a comparative longitudinal study. Proceedings of the Poster session presented at: 7th Joint ECTRIMS-ACTRIMS Meeting. 2017 Oct 25–28; Paris, France.	Study published outside of the timeframe of our review
Boster A, Nicholas J, Wu N, et al. Comparative Effectiveness Research of Disease-Modifying Therapies for the Management of Multiple Sclerosis: Analysis of a Large Health Insurance Claims Database. Neurol Ther. 2017;6(1):91-102.	Study published outside of the timeframe of our review

Citation	Decision
Chan A, Cohan S, Stark J, et al. Treatment with Delayed-release Dimethyl Fumarate is Associated with Fewer Relapses versus Glatiramer Acetate in Patients with Relapsing Remitting Multiple Sclerosis: Real-world Comparative Effectiveness Analyses from the EFFECT Study. Proceedings of the Poster session presented at: 7th Joint ECTRIMS-ACTRIMS Meeting. 2017 Oct 25–28; Paris, France P1160.	Study published outside of the timeframe of our review
Metin H. Huppertz H, Heymann R, Buchberger B. Adjusted indirect comparison of oral mutliple sclerosis agents. Value Health. 2015 Nov 1;18(7):A750.	Study published outside of the timeframe of our review
Hersh CM, Love TE, Cohn S, et al. Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 12-month follow-up. Mult Scler Relat Disord. 2016;10:44-52.	Study published outside of the timeframe of our review
Hersh CM, Love TE, Bandyopadhyay A, et al. Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 24-month follow-up. Mult Scler J Exp Transl Clin. 2017;3(3):2055217317715485.	Study published outside of the timeframe of our review
Spelman T, Kalincik T, Trojano M, et al. Comparative analysis of MS outcomes in dimethyl fumarate-treated patients relative to propensity matched fingolimod, interferon, glatiramer acetate, or teriflunomide. Mult Scler J. 2016; 22: 602–603.	Study published outside of the timeframe of our review
Cohn S et al. Presented at the 22nd Annual ECTRIMS Congress, 10-13 September 2014.	Study published outside of the timeframe of our review
Ontaneda D, Vollmer B, Sillau S, et al. Comparative efficacy and discontinuation of fingolimod and dimethyl fumarate in two large academic medical centers. Presented at the 2016 AAN Annual Meeting, 15-21, April 2016. Vancouver, Canada. P3.109.	Study published outside of the timeframe of our review
Sattarnezhad N, Healy BC, Baharnoori M, et al. Dimethyl fumarate versus interferon for treatment of relapsing-remitting multiple Sclerosis. Neurology. 2017; 88(16 suppl): P6.381.	Study published outside of the timeframe of our review
Sloane J, Phillips JT, Calkwood J, et al. Delayed-release dimethyl fumarate demonstrated no difference in clinical outcomes versus fingolimod in patients with relapsing-remitting multiple sclerosis: results from the real-world EFFECT study. Mult Scler J. 2017 Oct; 23: 855-856.	Study published outside of the timeframe of our review
Chan A, Cohan S, Stark J, et al. Treatment with delayed-release dimethyl fumarate is associated with fewer relapses versus glatiramer acetate in patients with relapsing remitting multiple sclerosis: real-world comparative effectiveness analyses from the EFFECT study.Mult Scler J. 2017 Oct; 23: 611.	Study published outside of the timeframe of our review
Viglietta V, Miller D, Bar-Or A, et al. Efficacy of delayed-release dimethyl fumarate in relapsing-remitting multiple sclerosis: integrated analysis of the phase 3 trials. Ann Clin Transl Neurol. 2015;2(2):103-118.	Study published outside of the timeframe of our review
Fox RJ, Gold R, Phillips JT, Okwuokenye M, Zhang A, Marantz JL. Efficacy and Tolerability of Delayed-release Dimethyl Fumarate in Black, Hispanic, and Asian Patients with Relapsing-Remitting Multiple Sclerosis: Post Hoc Integrated Analysis of DEFINE and CONFIRM. Neurol Ther. 2017;6(2):175-187.	Study published outside of the timeframe of our review

Citation	Decision
Berger T, Brochet B, Confalonieri P, et al. Effectiveness of delayed-release dimethyl fumarate on clinical measures and patient-reported outcomes in newly diagnosed and other early relapsing-remitting multiple sclerosis patients: Subgroup analysis of PROTEC. Presented at the 2017 AAN Annual Meeting, 22-28 April, 2017, Boston, MA.	Study published outside of the timeframe of our review
Kresa-Reahl K, Repovic P, Robertson D, Okwuokenye M, Meltzer L, Mendoza J. Clinical measures and impact on patient-reported outcomes of delayed-release dimethyl fumarate in relapsing multiple sclerosis patients after suboptimal response to glatiramer acetate: analysis of the 12-month RESPOND study. Mult Scler J. 2016; 22: 774.	Study published outside of the timeframe of our review
Lee A, Pike J, Edwards MR, Petrillo J, Waller J, Jones E. Quantifying the Benefits of Dimethyl Fumarate Over β Interferon and Glatiramer Acetate Therapies on Work Productivity Outcomes in MS Patients. Neurol Ther. 2017;6(1):79-90.	Study published outside of the timeframe of our review
Fox RJ, Chan A, Gold R, et al. Characterizing absolute lymphocyte count profiles in dimethyl fumarate-treated patients with MS: Patient management considerations. Neurol Clin Pract. 2016;6(3):220-229.	Study published outside of the timeframe of our review
Fox RJ, Chan A, Gold R, et al. Absolute lymphocyte count and lymphocyte subset profiles during long-term treatment with delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis. Mult Scler J. 2016; 22: 349.	Study published outside of the timeframe of our review
Williams MJ, Amezcua L, Okai A, et al. Real-World Safety and Effectiveness of Dimethyl Fumarate in Black or African American Patients with Multiple Sclerosis: 3-Year Results from ESTEEM [published online ahead of print, 2020 May 29]. Neurol Ther. 2020;10.1007/s40120-020-00193-5.	Study published outside of the timeframe of our review
Chinea A, Amezcua L, Vargas W, et al. Real-World Safety and Effectiveness of Dimethyl Fumarate in Hispanic or Latino Patients with Multiple Sclerosis: 3-Year Results from ESTEEM [published online ahead of print, 2020 May 29]. Neurol Ther. 2020;10.1007/s40120-020-00192-6.	Study published outside of the timeframe of our review
Gold R, Arnold DL, Bar-Or A, et al. Safety and efficacy of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: 9 years' follow-up of DEFINE, CONFIRM, and ENDORSE. Ther Adv Neurol Disord. 2020;13:1756286420915005.	Study published outside of the timeframe of our review
Chan A, Rose J, Alvarez E, Bar-Or A, Butzkueven H, Fox RJ, Gold R, Gudesblatt M, Haartsen J, Spelman T, Wright K. Lymphocyte reconstitution after DMF discontinuation in clinical trial and real-world patients with MS. Neurology: Clinical Practice. 2020; 10(5) 1-10.	Study published outside of the timeframe of our review
Buckle G, Bandari D, Greenstein J, et al. Effect of dimethyl fumarate on lymphocyte subsets in patients with relapsing multiple sclerosis. Mult Scler J Exp Transl Clin. 2020;6(2):2055217320918619.	Study published outside of the timeframe of our review

Appendix F. Humira

Appendix Table F1. References Submitted by AbbVie

Citation	Decision
Argyropoulou M, Kanni T, Kyprianou M, et al. Cost-savings of adalimumab in hidradenitis suppurativa: a retrospective analysis of a real-world cohort. Br J Dermatol. 2019;180(5):1161-1168.	Indication accounts for less than 10% of use
Kimball AB, Tzellos T, Calimlim BM, et al. Achieving Hidradenitis Suppurativa Response Score is Associated with Significant Improvement in Clinical and Patient-reported Outcomes: Post Hoc Analysis of Pooled Data From PIONEER I and II. Acta Derm Venereol. 2018;98(10):932-937.	Indication accounts for less than 10% of use
Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. J Am Acad Dermatol. 2019;80(1):60-69.e2.	Indication accounts for less than 10% of use
Gratacós J, Pontes C, Juanola X, et al. Non-inferiority of dose reduction versus standard dosing of TNF-inhibitors in axial spondyloarthritis. Arthritis Res Ther. 2019;21(1):11.	Indication accounts for less than 10% of use
Schofield D, Shrestha R, Cunich M. The economic impacts of using adalimumab (Humira®) for reducing pain in people with ankylosing spondylitis: A microsimulation study for Australia. Int J Rheum Dis. 2018;21(5):1106-1113.	Indication accounts for less than 10% of use
González-Fernández M, Villamañán E, Jiménez-Nácher I, et al. Cost evolution of biological agents for the treatment of spondyloarthritis in a tertiary hospital: influential factors in price. Int J Clin Pharm. 2018;40(6):1528-1538.	Indication accounts for less than 10% of use
Tzellos T, Song Y, Wang J, et al. A longitudinal assessment of the impact of adalimumab on work productivity, skin pain, and quality of life measures among patients with hidradenitis suppurativa. Poster presented at the 28th EADV Congress in Madrid, Spain. October 9-13 2019.	Indication accounts for less than 10% of use
Tzellos T, Sobell J, Ma J, et al. Patient-reported outcomes among patients with hidradenitis suppurative experiencing different levels of clinical response: integrated analysis from two clinical studies. J Am Acad Dermatol 2018;79(3_suppl 1):AB216.	Indication accounts for less than 10% of use
Bessette L, Khraishi M, Chow A, et al. Canadian adalimumab post-marketing observational epidemiological study assessing the effectiveness of adalimumab vs. non-biologic dmards in ankylosing spondylitis (COMPLETE-AS): 12-month effectiveness data. Ann Rheum Dis. 2018; 77: 1008-1009.	Indication accounts for less than 10% of use
Kaltsonoudis E, Pelechas E, Voulgari PV, Drosos A. Treatment of Rheumatoid arthritis with extension of the anti-TNF interdose intervals: A monocentric off-label study Ann Rheum Dis. 2019;78:2097.	Intervention/comparison outside our scope
Kaltsonoudis E, Pelechas E, Voulgari PV, Drosos AA. Prolongation or discontinuation of tumour necrosis factor inhibitors in the treatment of rheumatoid arthritis: Could this be a realistic scenario? Scand J Rheumatol. 2018;47:63-64.	Intervention/comparison outside our scope
Behrens F, Koehm M, Schwaneck EC, et al. Addition or removal of concomitant methotrexate alters adalimumab effectiveness in rheumatoid arthritis but not psoriatic arthritis. Scand J Rheumatol. 2019;48(5):375-382.	Intervention/comparison outside our scope

Citation	Decision
Bonca PD, Dolinar AL, Oblak M. A systematic Review of studies investigating the effectiveness of adalimumab patient support programmes. Ann Rheum Dis. 2019;78:2073-2074.	Intervention/comparison outside our scope
Brixner D, Rubin DT, Mease P, et al. Patient Support Program Increased Medication Adherence with Lower Total Health Care Costs Despite Increased Drug Spending. J Manag Care Spec Pharm. 2019;25(7):770-779.	Intervention/comparison outside our scope
Hawkes JE, Mittal M, Davis M, Brixner D. Impact of Online Prescription Management Systems on Biologic Treatment Initiation. Adv Ther. 2019;36(8):2021-2033.	Intervention/comparison outside our scope
Brixner D, Mittal M, Rubin DT, et al. Participation in an innovative patient support program reduces prescription abandonment for adalimumab-treated patients in a commercial population. Patient Prefer Adherence. 2019;13:1545-1556.	Intervention/comparison outside our scope
da Silva MRR, Dos Santos JBR, Almeida AM, et al. Effectiveness and safety of anti-TNF in psoriatic arthritis patients in Brazil: a post-incorporation analysis. J Comp Eff Res. 2018;7(10):989-1000.	Intervention/comparison outside our scope
Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial [published correction appears in Lancet. 2018 Dec 23;390(10114):2768]. Lancet. 2018;390(10114):2779-2789.	Intervention/comparison outside our scope
da Silva MRR, Dos Santos JBR, Almeida AM, et al. Biological therapy in the treatment of psoriatic arthritis: economic and epidemiological considerations. Expert Rev Clin Immunol. 2019;15(8):879-887.	Intervention/comparison outside our scope
Blauvelt A, Shi N, Zhu B, et al. Healthcare costs among psoriasis patients treated with ixekizumab or adalimumab J Manag Care Spec Pharm. 2019;25 (3a):S78.	Low-quality evidence
Song Y, Betts K, Singh R, et al. Economic evaluation of patients with psoriatic arthritis treated with adalimumab or secukinumab. J Manag Care Spec Pharm. 2018; 24 (4a): S80-S81.	Low-quality evidence
Aletaha D, Maa JF, Chen S, et al. Effect of disease duration and prior disease-modifying antirheumatic drug use on treatment outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2019;78(12):1609-1615.	Low-quality evidence
Hattori Y, Kojima T, Kaneko A, et al. High rate of improvement in serum matrix metalloproteinase-3 levels at 4 weeks predicts remission at 52 weeks in RA patients treated with adalimumab. Mod Rheumatol. 2018;28(1):119-125.	Low-quality evidence
Nakagawa H, Tanaka Y, Sano S, et al. Real-World Postmarketing Study of the Impact of Adalimumab Treatment on Work Productivity and Activity Impairment in Patients with Psoriatic Arthritis. Adv Ther. 2019;36(3):691-707.	Low-quality evidence
Chiorean M, Afzali A, Cross R, et al. Economic impact of switching from anti-TNF therapy to adalimumab, infliximab or other anti-TNF compared to switching from anti-TNF therapy to vedolizumab. Inflamm Bowel Dis. 2018 Feb; 24 (S1): S51-S52.	Outcomes not relevant to our scope
Behrens F, Koehm M, Schwaneck EC, et al. Use of a "critical difference" statistical criterion improves the predictive utility of the Health Assessment Questionnaire-Disability Index score in patients with rheumatoid arthritis. BMC Rheumatol. 2019;3:51.	Outcomes not relevant to our scope
Landewé R, Ritchlin CT, Aletaha D, et al. Inhibition of radiographic progression in psoriatic arthritis by adalimumab independent of the control of clinical disease activity. Rheumatology (Oxford). 2019;58(6):1025-1033.	Outcomes not relevant to our scope
Donahue KE, Schulman ER, Gartlehner G, et al. Comparative Effectiveness of Combining MTX with Biologic Drug Therapy Versus Either MTX or Biologics	Outcomes not relevant to our scope

Citation	Decision
Alone for Early Rheumatoid Arthritis in Adults: a Systematic Review and Network Meta-analysis [published correction appears in J Gen Intern Med. 2020 May 26;:]. J Gen Intern Med. 2019;34(10):2232-2245.	
Armstrong AW, Betts KA, Signorovitch JE, et al. Number needed to treat and costs per responder among biologic treatments for moderate-to-severe psoriasis: a network meta-analysis. Curr Med Res Opin. 2018;34(7):1325-1333.	Outcomes not relevant to our scope
Fagerli KM, Kearsley-Fleet L, Watson KD, et al. Long-term persistence of TNF-inhibitor treatment in patients with psoriatic arthritis. Data from the British Society for Rheumatology Biologics Register. RMD Open. 2018;4(1):e000596.	Outcomes not relevant to our scope
MacDougall D, Griffith J, Ehrenberg R, et al. Greater than expected dosing (GTED) assessment among targeted immunomodulators in management of inflammatory bowel disease (IBD). J Manag Care Spec Pharm 2019;25(3a):S76.	Outcomes not relevant to our scope
Garcia-Porrua C, Maceiras-Pan F, Fernandez-Dominguez L, et al. Drug survival on first tnf inhibitors in patients with psoriatic arthritis: comparison across etanercept, adalimumab, golimumab and infliximab. Ann Rheum Dis. 2018;77:1031.	Outcomes not relevant to our scope
Beilman CL, Fedorak RN, Halloran BP. Cost-effectiveness of vedolizumab, infliximab, and adalimumab as first-line therapy for ulcerative colitis. Gastroenterology. 2019;154(6):S-450; 450.	Outcomes not relevant to our scope
Savage LJ, Dasgupta D, Reyes-Servin O, Calimlim B. Response to adalimumab in patients with plaque psoriasis by associated manifestations: analyses from the British Association of Dermatologists Biologics and Immunomodulators Register. J Eur Acad Dermatol Venereol. 2019; 33 (S3): 4.	Previously known information about adalimumab related to efficacy
Strand V, Husni ME, Griffith J, et al. Network Meta-Analysis of Targeted Immunomodulators in the Treatment of Psoriatic Arthritis Patients without Prior Biologic Treatment. Arthritis & Rheumatology. 2018 Sep; 70 (S10): 701.	Previously known information about adalimumab related to efficacy
Khraishi M, Bessette L, Chow A, et al. Canadian adalimumab post-marketing observational epidemiological study assessing the effectiveness of adalimumab vs non-biologic DMARDs in psoriatic arthritis (complete-PSA): 12-month effectiveness data. Ann Rheum Dis. 2018;77:1592.	Previously known information about adalimumab related to efficacy
Muñoz-Villafranca C, Ortiz de Zarate J, Arreba P, et al. Adalimumab treatment of anti-TNF-naïve patients with ulcerative colitis: Deep remission and response factors. Dig Liver Dis. 2018;50(8):812-819.	Previously known information about adalimumab related to efficacy
Kaeley GS, MacCarter DK, Goyal JR, et al. Similar Improvements in Patient-Reported Outcomes Among Rheumatoid Arthritis Patients Treated with Two Different Doses of Methotrexate in Combination with Adalimumab: Results From the MUSICA Trial. Rheumatol Ther. 2018;5(1):123-134.	Previously known information about adalimumab related to efficacy
Savage LJ, Garcia-Horton V, Li J, et al. Number needed to treat and cost per responder to flexible adalimumab dosing in the treatment of psoriasis in patients with suboptimal response to 40mg every other week dosing. J Eur Acad Dermatol Venereol. 2019;33:3-4.	Previously known information about adalimumab related to efficacy
Van Den Bosch F, Wassenberg S, Zueger P, et al. Impact of prior biologic use on treatment response in patients with rheumatoid arthritis receiving adalimumab in routine clinical care: results from the passion study. J Clin Rheumatol. 2019;25(3):S54.	Previously known information about adalimumab related to efficacy
Panaccione R, Colombel JF, Bossuyt P, et al. Tight control with adalimumab-based treatment is associated with improved quality of life outcomes in patients with moderate to severely active Crohn's disease: data from CALM. J Crohns Colitis. 2018 Jan 16;12(S1):S078-9.	Previously known information about adalimumab related to efficacy

Citation	Decision
Loftus EV, Reinisch W, Panaccione R, et al. Adalimumab Effectiveness Up to Six Years in Adalimumab-naïve Patients with Crohn's Disease: Results of the PYRAMID Registry. Inflamm Bowel Dis. 2019;25(9):1522-1531.	Previously known information about adalimumab related to efficacy
Louis EJ, Reinisch W, Schwartz DA, et al. Adalimumab Reduces Extraintestinal Manifestations in Patients with Crohn's Disease: A Pooled Analysis of 11 Clinical Studies. Adv Ther. 2018;35(4):563-576.	Previously known information about adalimumab related to efficacy
Lu C, Wallace BI, Waljee AK, et al. Comparative efficacy and safety of targeted DMARDs for active psoriatic arthritis during induction therapy: A systematic review and network meta-analysis. Semin Arthritis Rheum. 2019;49(3):381-388.	Previously known information about adalimumab related to efficacy
Murray E, Ellis A, Butylkova Y, et al. Systematic review and network meta-analysis: effect of biologics on radiographic progression in rheumatoid arthritis. J Comp Eff Res. 2018;7(10):959-974.	Previously known information about adalimumab related to efficacy
Smolen JS, van Vollenhoven RF, Florentinus S, et al. Predictors of disease activity and structural progression after treatment with adalimumab plus methotrexate or continued methotrexate monotherapy in patients with early rheumatoid arthritis and suboptimal response to methotrexate. Ann Rheum Dis. 2018;77(11):1566-1572.	Previously known information about adalimumab related to efficacy
Strand V, Elaine Husni M, Betts KA, et al. Network meta-analysis and cost per responder of targeted Immunomodulators in the treatment of active psoriatic arthritis. BMC Rheumatol. 2018;2:3.	Previously known information about adalimumab related to efficacy
Popp RA, Rascati K, Davis M, Patel U. Refining a Claims-based Algorithm to Estimate Biologic Medication Effectiveness and Cost per Effectively Treated Patient with Rheumatoid Arthritis. Pharmacotherapy. 2018;38(2):172-180.	Previously known information about adalimumab related to efficacy
Imafuku S, Nakano A, Dakeshita H, et al. Number needed to treat and costs per responder among biologic treatments for moderate-to-severe plaque psoriasis in Japan. J Dermatolog Treat. 2018;29(1):24-31.	Previously known information about adalimumab related to efficacy
Panaccione R, Sandborn WJ, D'Haens G, et al. Clinical Benefit of Long-Term Adalimumab Treatment in Patients With Crohn's Disease Following Loss of Response or Intolerance to Infliximab: 96-Week Efficacy Data From GAIN/ADHERE Trials. J Crohns Colitis. 2018;12(8):930-938.	Previously known information about adalimumab related to safety
Strober B, Crowley J, Langley RG, et al. Systematic review of the real-world evidence of adalimumab safety in psoriasis registries. J Eur Acad Dermatol Venereol. 2018;32(12):2126-2133.	Previously known information about adalimumab related to safety
Wu JJ, Abramovits W, Kerdel F, et al. Eight-year interim results from the ESPRIT ten-year postmarketing surveillance registry of adalimumab for moderate to severe psoriasis J Am Acad Dermatol. 2018;79(3):AB126.	Previously known information about adalimumab related to safety
Loftus EV, Reinisch W, Panaccione R, et al. Long-Term Effectiveness and Safety of Adalimumab Based on Crohn's Disease Duration: Results from the PYRAMID Registry. J Crohns Colitis. 2018 Jan; 12 (S1): S493-494.	Previously known information about adalimumab related to safety
Emery P, Burmester GR, Naredo E, et al. Design of a phase IV randomised, double-blind, placebo-controlled trial assessing the ImPact of Residual Inflammation Detected via Imaging TEchniques, Drug Levels and Patient Characteristics on the Outcome of Dose TaperIng of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) patients (PREDICTRA). BMJ Open. 2018;8(2):e019007.	Study protocol
Harrold LR, Griffith J, Zueger P, et al. Longterm, Real-world Safety of Adalimumab in Rheumatoid Arthritis: Analysis of a Prospective US-based Registry. J Rheumatol. 2020;47(7):959-967.	Study published outside of the timeframe of our review
Spivey CA, Winthrop KL, Griffith J, et al. Retrospective Analysis of the Impact of Adalimumab Initiation on Corticosteroid Utilization and Medical Costs Among	Study published outside of the timeframe of our review

Citation	Decision
Biologic-Naïve Patients with Rheumatoid Arthritis. Rheumatol Ther. 2020;7(1):133-147.	
McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial [published correction appears in Lancet. 2020 May 30;395(10238):1694]. Lancet. 2020;395(10235):1496-1505.	Study published outside of the timeframe of our review
Panaccione R, Colombel JF, Travis SPL, et al. Tight control for Crohn's disease with adalimumab-based treatment is cost-effective: an economic assessment of the CALM trial. Gut. 2020;69(4):658-664.	Study published outside of the timeframe of our review

Appendix G. Entresto

Appendix Table G1. References Submitted by Novartis

Citation	Decision
Ambrosy AP, Braunwald E, Morrow DA, et al. Angiotensin receptor-neprilysin inhibition in acute decompensated heart failure based on prior exposure to a conventional renin-angiotensin system antagonist. Poster presented at the American College of Cardiology Annual Meeting; March 16-18, 2019; New Orleans, Louisiana.	Conference citation – abstract/full presentation not provided
Drazner MH. Angiotensin receptor-neprilysin inhibition (ARNI) therapy and reverse remodeling in heart failure with reduced ejection fraction. JAMA. 2019;322(11):1051-1053.	Editorial
Januzzi JL Jr, Prescott MF, Butler J, et al. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction (PROVE-HF). JAMA. 2019;322(11):1-11.	Low-quality evidence
Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail. 2019;21(8):998-1007.	Low-quality evidence
Desai AS, Solomon SD, Shah AM, et al. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction (EVALUATE-HF). JAMA. 2019;322(11):1077-1084.	New evidence of no clinical improvement with sacubitril/valsartan
Albert NM, Swindle JP, Buysman EK, Chang C. Lower hospitalization and healthcare costs with sacubitril/valsartan versus angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker in a retrospective analysis of patients with heart failure. J Am Heart Assoc. 2019;8(9):e011089.	Previously known information about sacubitril/valsartan related to efficacy
Greene SJ, Lippmann SJ, Mentz RJ, et al. Clinical effectiveness of sacubitril/valsartan among patients hospitalized for heart failure with reduced ejection fraction. J Card Fail. 2019;25(11):P937.	Previously known information about sacubitril/valsartan related to efficacy
Khariton Y, Fonarow GC, Arnold SV, et al. Association between sacubitril/valsartan initiation and health status outcomes in heart failure with reduced ejection fraction. JACC Heart Fail. 2019;7(11):933-941.	Previously known information about sacubitril/valsartan related to efficacy
Ambrosy AP, Braunwald E, Morrow DA, et al. Angiotensin receptor-neprilysin inhibition based on history of heart failure and use of renin-angiotensin system antagonists. J Am Coll Cardiol. 2020;76(9):1034-48.	Study published outside of the timeframe of our review
Burke J, Sahli B, Gleason P. Sacubitril-valsartan real-world assessment of total cost of care and resource utilization pre/post initiation among commercially insured members with reduced ejection fraction heart failure. J Manag Care Spec Pharm. 2020 Oct; 26 (10a): S14.	Study published outside of the timeframe of our review
Gaziano TA, Fonarow GC, Claggett B, et al. Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure with reduced ejection fraction. J Am Heart Assoc. 2016;1(6):666-672.	Study published outside of the timeframe of our review
Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of sacubitril-valsartan in hospitalized patients who have heart failure with reduced ejection fraction [published online ahead of print August 12, 2020]. JAMA Cardiol. 2020. doi:10.1001/jamacardio.2020.2822	Study published outside of the timeframe of our review
Shaddy R, Canter C, Halnon N, et al. Design for the sacubitril/valsartan (LCZ696) compared with enalapril study of pediatric patients with heart failure	Study published outside of the timeframe of our review

Citation	Decision
due to systemic left ventricle systolic dysfunction (PANORAMA-HF study). Am Heart J. 2017;193:23-34.	
Tan NY, Sangaralingham LR, Sangaralingham SJ, Yao X, Shah ND, Dunlay SM. Comparative effectiveness of sacubitril-valsartan versus ACE/ARB therapy in heart failure with reduced ejection fraction. JACC Heart Fail. 2020;8(1):43-54.	Study published outside of the timeframe of our review
Yancy CW, Hernandez AF, Bonow RO. The use of sacubitril/valsartan for hospitalized heart failure—why do we care about cost and value? [published online ahead of print August 12, 2020]. JAMA Cardiol. 2020. doi:10.1001/jamacardio.2020.3108.	Study published outside of the timeframe of our review

Appendix H. Vimpat

Appendix Table H1. References Submitted by UCB

Citation	Decision
Rosenow F, Winter Y, Leunikava I, et al. Patient preference in epilepsy monotherapy prior to physician consultation: Real-world interim data from a multinational noninterventional study. ILAE-UK 2019. 2019: abstract.	Intervention/comparison not relevant to scope
Potter B, Beller C, Borghs S, et al. Safety, tolerability, and cognitive and behavioral effects of long-term adjunctive Vimpat in children and adolescents with focal seizures. Neurology. 2018; 90 (15S): abstract P1.027.	Previously known information about lacosamide related to safety
Wu T, Chuang YC, Huang HC, et al. A multicenter, observational trial in Taiwan to evaluate the safety and tolerability of Vimpat in clinical practice for the treatment of epilepsy. AES 2019. 2019: abstract 1.307.	Previously known information about lacosamide related to safety
Inoue Y, Du X, Hoshii N, Sasamoto H. Safety and efficacy of adjunctive Vimpat in Chinese and Japanese adult epilepsy patients with focal seizures: Interim data from an open-label extension trial. Epilepsia; 2019; 60 (S2): 62.	Previously known information about lacosamide related to safety
Hong Z, Du X, Liao W, et al. Efficacy and safety of Vimpat as adjunctive therapy in Chinese patients with partial-onset seizures: subgroup and post hoc analyses of a randomized double-blind trial and open-label extension. Chin J Clin Neurosci. 2019; 27(4): 361-378.	Previously known information about lacosamide related to efficacy
Ruda R, Hellot S, De Baacker M, et al. Non-interventional study of adjunctive vimpat therapy in patients with brain tumor-related epilepsy. Neurology. 2019; 92(15S): abstract S30.006.	Previously known information about lacosamide related to efficacy
Ruda R, Hellot S, De Baacker M, et al. Effectiveness and tolerability of Vimpat as add-on therapy in patients with brain tumor-related epilepsy: Results from a prospective, non-interventional study in European clinical practice. Neuro Oncol. 2019; 21 (S3): iii20-iii21.	Previously known information about lacosamide related to efficacy
Ruda R, Hellot S, De Baacker M, et al. Effectiveness and tolerability of adjunctive Vimpat in patients with brain tumour-related epilepsy: a prospective, non-interventional study in European clinical practice. ILAE-UK 2019. 2019: abstract.	Previously known information about lacosamide related to efficacy
Inoue Y, Du X, Sasamoto H, et al. Open-label, long-term extension study evaluating the safety and efficacy of adjunctive Vimpat in Chinese and Japanese adults with focal seizures: 1-year interim results. AOEC abstract; 2016.	Study published outside of the timeframe of our review
Tanaka S, Inoue Y, Terada K, et al. Adjunctive Vimpat for the treatment of drug-resistant partial-onset seizures in Chinese and Japanese adults: A randomized, placebo-controlled Phase III study and extension study. JES abstract; 2016.	Study published outside of the timeframe of our review
Inoue Y, Osakabe T, Hirano K, Shimizu S. Tolerability of adjunctive therapy with Vimpat, a novel antiepileptic drug, in adult epilepsy patients: Secondary analysis of data from a double-blind comparative trial and an ongoing long-term open trial. Japan J Clin Psychopharm. 2017; 20 (4): 439-453.	Study published outside of the timeframe of our review
Yuen N, Taeter C, Beller C, et al. Tolerability of adjunctive Vimpat in paediatric patients aged 4 to <16 years with focal seizures: an interim pooled analysis of data from open-label trials. Epilepsia. 2017; 58 (S5): S132.	Study published outside of the timeframe of our review

Citation	Decision
Yuen N, Taeter C, Beller C, et al. Long-term tolerability of adjunctive Vimpat in pediatric patients aged 4 to <16 years with focal seizures: an interim pooled analysis of data from open-label trials. AES 2017. 2017; abstract 1.282.	Study published outside of the timeframe of our review
Farkas V, Beller C, McClung C, et al. Safety and tolerability of intravenous Vimpat in children with epilepsy: an open-label trial. CNS 2020. 2020: abstract [accepted].	Study published outside of the timeframe of our review
Ferreira JA, Pina-Garza JE, Rice K, et al. Long-term safety and tolerability of adjunctive Vimpat in children with focal epilepsy: interim results from an open-label trial. AES 2016; 2016: abstract 1.269.	Study published outside of the timeframe of our review
Yuen N, Taeter C, Beller C, et al. Tolerability of adjunctive Vimpat in paediatric patients aged 4 to <16 years with focal seizures: an interim pooled analysis of data from open-label trials. Epilepsia. 2017; 58 (S5): S132.	Study published outside of the timeframe of our review
Oshima Y, Nakashima K, Hirano K. Safety and efficacy of oral Vimpat as adjunctive therapy in clinical practice: Interim analysis of the post-marketing surveillance in adults with focal-onset seizures. Shinryo to Shinyaku (Med Cons New-Remed). 2020; 57 (2): 98-108.	Study published outside of the timeframe of our review
Warnock R, Yates S, Schmid M, et al. Rationale and study design for a novel Phase-III, randomized, double-blind trial of adjunctive Vimpat in patients with idiopathic generalized (genetic) epilepsy and uncontrolled primary generalized tonic-clonic seizures. Epilepsia. 2016; 56 (S1): 215.	Study published outside of the timeframe of our review
Steiniger-Brach B, Vossler D, Knake S, et al. Efficacy and tolerability of adjunctive Vimpat in the treatment of primary generalized tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. FENS 2020. 2020; abstract.	Study published outside of the timeframe of our review
Vossler DG, Knake S, O'Brien TJ, et al. Efficacy and tolerability of adjunctive Vimpat in the treatment of primary generalized tonic-clonic seizures: a double-blind, randomized, placebo-controlled trial. DGfE 2020. 2020; abstract [accepted].	Study published outside of the timeframe of our review
NG YT, Vossler DG, Knake S, et al. Efficacy and tolerability of adjunctive Vimpat in the treatment pf pediatric patients with primary generalized tonic-clonic seizures: subgroup analysis of a double-blind, randomized, placebo-controlled trial. CNS 2020. 2020; abstract [accepted].	Study published outside of the timeframe of our review
Vossler DG, Knake S, O'Brien TJ, et al. Efficacy and safety of adjunctive Vimpat in the treatment of primary generalised tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. J Neurol Neurosurg Psychiatry. 2020: [ACCEPTED].	Study published outside of the timeframe of our review
Ruda R, Houillier C, Maschio M, et al. Effectiveness and tolerability of Vimpat as add-on therapy in patients with brain tumor-related epilepsy: Results from a prospective, non-interventional study in European clinical practice (VIBES). Epilepsia. 2020; 61 (4): 647-656.	Study published outside of the timeframe of our review
Allard J, Henley W, Mclean B, et al. Vimpat in the general population and in people with intellectual disability: similar responses? Seizure. 2020; 76: 161-166.	Study published outside of the timeframe of our review
Farkas V, Steinborn B, Flamini J, et al. Efficacy and tolerability of adjunctive Vimpat in children and adolescents with uncontrolled seizures: A randomized, double-blind, placebo-controlled tiral. Ann Neur. 2017; 82 (S21): S287-S290.	Study published outside of the timeframe of our review

Appendix I. Entyvio

Appendix Table I1. References Submitted by Takeda

Citation	Decision
Bressler B, Yarur A, Kopylov U, et al. Clinical effectiveness of first-line anti-TNF therapies and second-line anti-TNF therapy post-vedolizumab discontinuation in patients with ulcerative colitis or Crohn's disease. Am J Gastroenterol. 2019 Oct; 114: S373	Intervention/comparison not relevant to our scope
Bohm M, Sagi SV, Fischer M, et al. Comparative effectiveness of vedolizumab and tumour necrosis factor-antagonist therapy in Crohn's disease: a multicenter consortium propensity score-matched analysis. J Crohns Colitis. 2018; 12(S1):S018	Low-quality evidence
Lukin D, Weiss A, Aniwan S, et al. Comparative safety profile of vedolizumab and tumour necrosis factor–antagonist therapy for inflammatory bowel disease: a multicentre consortium propensity score-matched analysis. J Crohns Colitis. 2018; 12(S1):S036	Low-quality evidence
Faleck D, Shashi P, Meserve J, et al. Comparative effectiveness of vedolizumab and TNF-antagonist therapy in ulcerative colitis: a multicentre consortium propensity score matched analysis. J Crohns Colitis. 2018; 12(S1):S019	Low-quality evidence
Meserve J, Aniwan S, Koliani-Pace JL, et al. A multicentre cohort study to assess the safety of vedolizumab for inflammatory bowel disease. J Crohns Colitis. 2018; 12(S1): S034	Low-quality evidence
Yarur A, Mantzaris GJ, Kopylov U, et al. Real world safety of vedolizumab and anti-TNF therapies in biologic naïve ulcerative colitis and crohn's disease patients: Results from the EVOLVE study. Am J Gastroenterol. 2019 Oct; 114: S460	Low-quality evidence
Koliani-Pace JL, Singh S, Luo M et al. Changes in Vedolizumab Utilization Across US Academic Centers and Community Practice Are Associated With Improved Effectiveness and Disease Outcomes. Inflamm Bowel Dis. 2019;25(11):1854–1861	Low-quality evidence
Meserve J, Aniwan S, Koliani-Pace JL et al. Retrospective analysis of safety of vedolizumab in patients with inflammatory bowel diseases. Clin Gastr Hep. 2019;17(8):1533-1540.e2	Previously known information about vedolizumab related to safety
Narula N, Peerani F, Meserve J et al. Vedolizumab for Ulcerative Colitis: Treatment Outcomes from the VICTORY Consortium. Am J Gastroenterol. 2018; 113(9): 1345	Previously known information about vedolizumab related to efficacy
Vermeire S, Colombel JF, Feagan BG, et al. Long-term safety of vedolizumab in ulcerative colitis and Crohn's disease: final results from the GEMINI LTS study. J Crohns Colitis. 2019 Mar; 13 (S1): S018-S020.	Previously known information about vedolizumab related to safety
Loftus EV, Colombel JF, Feagan BG, et al. Long-Term Safety of Vedolizumab in Ulcerative Colitis and Crohn's Disease: Final Results from the Gemini Lts Study. Gastroenterology. 2019 May; 156 (6S): S182	Previously known information about vedolizumab related to safety
Card T, Ungaro R, Bhayat F, Blake A, Hantsbarger G, Travis S. Vedolizumab use is not associated with increased malignancy incidence: GEMINI LTS study results and post-marketing data. Aliment Pharmacol Ther. 2020;51(1):149-157.	Study published outside of the timeframe of our review

Appendix J. Xtandi

Appendix Table J1. References Submitted by Astellas

Citation	Decision
Schultz NM, Flanders SC, Wilson S, et al. Treatment Duration, Healthcare Resource Utilization, and Costs Among Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Enzalutamide or Abiraterone Acetate: A Retrospective Claims Analysis. Adv Ther. 2018;35(10):1639-1655.	Outcomes not relevant to scope of review
Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2020;382(23):2197-2206.	Study published outside of the timeframe of our review
Schultz NM, O'Day K, Sugarman R, Ramaswamy K. Budget Impact of Enzalutamide for Nonmetastatic Castration-Resistant Prostate Cancer. J Manag Care Spec Pharm. 2020;26(4):538-549.	Study published outside of the timeframe of our review
Stenzl A, Dunshee C, De Giorgi U, et al. Effect of Enzalutamide plus Androgen Deprivation Therapy on Health-related Quality of Life in Patients with Metastatic Hormone-sensitive Prostate Cancer: An Analysis of the ARCHES Randomised, Placebo-controlled, Phase 3 Study [published online ahead of print, 2020 Apr 23]. Eur Urol. 2020;S0302-2838(20)30194-9.	Study published outside of the timeframe of our review
Ramaswamy K, Lechpammer S, Mardekian J, et al. Economic Outcomes in Patients with Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer Treated with Enzalutamide or Abiraterone Acetate Plus Prednisone. Adv Ther. 2020;37(5):2083-2097.	Study published outside of the timeframe of our review

Appendix K. ICER Responses to Manufacturer Comments

General Evidence Response (GER): Many public comments from manufacturers focused on the evaluation and interpretation of evidence within the ICER UPI Report. The following is a combined response to such questions and comments. This should allow all stakeholders to see, in a single place, how ICER is thinking about evidence with regard to the UPI Report. Additionally, to avoid redundancy we will respond to some individual public comments by referencing one or more of the sections below.

1. New clinical evidence
    a. Over a two-year period, there will virtually always be new published information about widely used medications. However, for ICER to consider such information as potentially providing support for a price increase there must be some question that was evaluated such that there is an answer that could be counted, a priori, as **not** supporting a price increase had the results come out differently. For instance, if the HR for survival with a therapy has been shown to be 0.72 with four years of follow-up and at eight years of follow-up the HR is now calculated to be 0.75, there must have been a prior belief about what that HR might have been at eight years for this to be assessed as to whether it supports a price increase. Without that prior belief, we are unable to know whether this is a favorable or unfavorable result for the drug under consideration.
    b. New evidence must provide information different from what was previously believed to support a price increase. In the example above, if it were assumed that the HR for survival would persist over time, and at eight years of follow-up the HR was again 0.75, this would not be considered support. In contrast, had there been serious reasons for concern that the effect of therapy decreased substantially over time, a HR of 0.75 at eight years could provide support.
2. Real-world evidence (RWE)
    a. ICER applies the same evidentiary standards to RWE that it applies to all other forms of evidence and is happy to consider RWE as part of the UPI Report.
    b. High-quality RWE can be particularly valuable in assessing effectiveness of therapies and issues around adherence.
3. Quality of observational evidence
    a. As noted in the UPI Protocol, ICER only reviewed observational studies as part of the UPI Report process that were submitted by manufacturers.
    b. As noted in the UPI Protocol, ICER is using GRADE to assess quality of evidence. Most high-quality comparative observational studies generate only low-quality evidence using GRADE for the comparison being assessed. That is, the quality of the observational studies is only one factor that goes into assessing the quality of the

evidence provided by those studies. Factors that can sometimes increase the quality of evidence from high-quality observational studies include large (or very large) magnitude of effect, dose response, or all plausible residual confounding working opposite to the effect being seen.

4. Modeling and meta-analyses
    a. Models and meta-analyses provide ways of interpreting and combining evidence but are not new evidence in and of themselves. Occasionally, models and meta-analyses lead to a new understanding of evidence that is substantially different from what was previously believed. Under these circumstances, models and meta-analyses could contribute as "new evidence" within the UPI Report.
    b. Economic outcomes are explicitly part of the UPI process and can count as new clinical evidence if the results are different from what had been previously believed.
5. Importance of studies
    a. As discussed in the Introduction, ICER recognizes that studies and trials that confirm prior beliefs, increase quality of evidence, and examine new aspects of a therapy's benefits are vitally important. Nothing in the UPI Report should be taken to suggest that studies that fail to support large price increases of the most expensive drugs used in the US are somehow not worth having been performed. That is not the bar that UPI is using. The UPI Report is assessing the fairness of price increases, not the value of research.
    b. Studies evaluating the benefits of a therapy in a small population are also clearly important. ICER does not believe, however, that demonstrating new benefits in a small population justifies large price increases in the most expensive drugs.

#	Comment	Response/Integration
AbbVie		
1.	As a company committed to ongoing research and development, AbbVie believes in the growing body of clinical, economic, and humanistic evidence and that every piece of evidence, whether from randomized studies, real-world evidence, long-term follow-up, or economic studies advances the clinical community's understanding of both HUMIRA and the diseases it treats. It is in this spirit that we submitted 58 references to publications over the prior two years (beginning of 2018 through the end of 2019) for ICER's consideration. By excluding high-quality evidence from its assessment ICER cannot assess the totality of research available to demonstrate the value of a product to patients, physicians, and payers. We believe these additional publications contribute to the body of evidence supporting the net health benefit of HUMIRA that should be considered.	Please see GER 5a.
2.	In limiting the assessment to indications representing greater than 10 percent use, ICER excluded HUMIRA's clinical and economic evidence in smaller patient populations, including rare conditions and pediatric populations that reflect our commitment to innovation and improvement in net health benefit to underserved populations with high unmet needs. … In limiting the UPI assessment to only those indications representing greater than 10 percent of use, ICER excluded evaluation of clinical, economic and/or humanistic evidence for rare conditions and pediatric indications. AbbVie disagrees with a methodology that discounts the investment in improving clinical practice and advancing standard of care and value provided to pediatric patients and patients suffering from rare diseases, simply because such patients are fewer in number. Just as FDA incentivizes the development of evidence regarding the treatment of orphan and rare diseases, ICER should acknowledge and consider in its assessment the value of investing in smaller, yet high burden, disease areas.	Please see GER 5a, 5b.
3.	The assessment does not appropriately account for AbbVie's dedication to patient access and continued investment and innovation in HUMIRA through the development of patient-centric programs.	Please see GER 5a.
Amgen		
1.	ICER should consider the SEAM-PsA trial as meaningful new evidence and recalibrate its assessment of these data as supportive of Enbrel's price increase.	We have expanded our description of our reasoning with regard to etanercept and

	The SEAM-PsA randomized clinical trial (which was published after the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) Guideline for the Treatment of Psoriatic Arthritis)[i] qualifies as *new evidence.* ICER's 2019 UPI Report determined that two products, Genvoya® and Revlimid® did not have unsupported price increases: this was based on clinical evidence for these two products that is no different from the clinical evidence for Enbrel. The SEAM-PsA trial provides improved clinical evidence that shifted the evidence base and the understanding of the magnitude of net benefit, which was previously considered "*Low- to very low-quality evidence*" in the 2018 ACR/NSF guideline which was published while the SEAM-PsA trial was ongoing. Prior studies referenced by ICER as justification to exclude SEAM-PsA [CHAMPION, RESTORE1, RESPOND] should be disregarded. These studies either utilized incomparable endpoints [i.e., PASI versus ACR20] or were in combination with methotrexate (MTX) versus monotherapy and involved different anti-TNF therapies. • ACR20 is a core outcome measure that is of direct importance to patients that was excluded in CHAMPION and RESTORE. • The RESPOND study did not establish anti-TNFs as a monotherapy for use in treatment naïve PsA patients.	the SEAM-PsA trial. This is a close call and we have stated this in the UPI Report.
2.	ICER's selected trials also involved different anti-TNFs with key immunogenicity differences such as the development of anti-drug antibodies (ADAs). ADA formation leads to loss of efficacy and is associated with lower ACR20 response, where drugs such as infliximab and adalimumab result in therapeutic failure due to ADAs in various autoimmune diseases like rheumatoid arthritis, spondylarthritis, and Crohn's disease. The RESTORE/RESPOND and CHAMPION studies involved infliximab and adalimumab, respectively. Studies have shown that ADA development has been associated with decreased clinical efficacy in these two monoclonal antibody TNF inhibitors: (*e.g.*, antibodies against infliximab were correlated with decreased clinical response in five studies, and anti-adalimumab antibodies corresponded with lower clinical efficacy in 3 out of 5 studies). In contrast, Enbrel studies have shown minimal development of ADAs and furthermore, the ADAs against Enbrel were non-neutralizing and not associated with any apparent effects on clinical response.	Studies looking at surrogate outcomes only occasionally provide high- or moderate-quality evidence of a substantial new benefit.
Astellas		
1.	ICER initially estimated a net price increase for XTANDI of 15.9% and a corresponding estimated spend increase of $230 million.	We do not feel the email record supports Astellas' statement of events. ICER would,

	Early on and on several occasions through the assessment period, Astellas provided corrected data to ICER on net price increase of 2.5% during the period between 2018 and 2019. It was only after the final manufacturer input period that ICER requested the additional data point for increase in drug spending which Astellas provided (estimated $37 million). ICER subsequently adjusted its calculations and confirmed that XTANDI moved much further down in the list of drugs under consideration for the UPI Report, to no longer be in the top 10. However, ICER has continued to include XTANDI in the assessment even after acknowledging that XTANDI does not meet the criteria established in ICER's 2020 UPI Protocol. ICER's 2020 UPI Protocol provided an established and detailed process for determining which drug products would be included in the UPI Report. The 2020 Protocol provided that, "[a]fter resolution of any concerns about estimates, the top 10 drugs remaining on the list will constitute the final list of drugs for which the evidence review will be undertaken." While Astellas commends ICER's correction of its initial net price increase and spend estimates for XTANDI, we disagree with XTANDI's inclusion in the 2020 UPI Report (which is contrary to ICER's 2020 UPI Protocol).	of course, have acted earlier had Astellas provided the requested information. When Astellas, long past the date set in the UPI Protocol, provided information that placed Xtandi at position 11 in the report, we kept it in the assessment but described the corrected position in the report. The 2020 UPI Protocol states, "ICER continues to expect that situations may arise that were not fully anticipated in this protocol and recognizes that it may need to alter aspects of the review to maintain transparency and fairness to all parties." We believe we are acting in alignment with this statement.
Biogen		
1.	Eight of the 17 studies published in 2018-2019 were comparative effectiveness studies that consistently demonstrate that TECFIDERA has superior clinical outcomes compared to glatiramer acetate, teriflunomide, and interferons and has similar outcomes to fingolimod. Results from various other prospective, observational studies submitted also demonstrate TECFIDERA's significant impact on quality of life, health care resource utilization, and other patient-reported outcomes (PROs) for patients with MS. Biogen respectfully disagrees with the exclusion for these studies as they provide important new and confirmatory clinical information on TECFIDERA. While observational studies do not always merit a similar quality grade to that of RCTs, it is disappointing that all observational studies in the TECFIDERA assessment have been excluded in this report as they can inform clinical care. Excluding these studies dismisses a large volume of previously unpublished, peer-reviewed, scientific evidence, often for different patient subgroups, follow-up duration, data sources, and/or countries,	Please see GER 3b, 5a.

	consistently showing that TECFIDERA has superior outcomes as compared to teriflunomide, glatiramer acetate, and interferons and has similar outcomes as compared to fingolimod.	
2.	ICER's reliance on the GRADE method for evaluation of evidence is inconsistent with the evolution of key stakeholders' sources of evidence and increasing emphasis on use of real-world research. Furthermore, payers, clinicians, and regulators increasingly look to well-conducted observational studies to address existing evidence gaps, such as efficacy in populations not previously studied in RCTs due to rigid inclusion/exclusion criteria.	Please see GER 2a, 2b, 3b. Additionally, we feel that GRADE is an internationally accepted standard.
3.	Biogen strongly recommends that ICER re-evaluate the observational studies supporting the benefits of TECFIDERA and consider approaches for assessing the value of real-world, observational research, which is an important element to inform clinical decision-making and patient care. Reports such as these have the potential to devalue or reduce incentives for manufacturers to generate more evidence on the value of therapies, thus limiting the evidence available to improve decision-making.	Please see GER 5a.
4.	Multiple prospective, observational, or interventional studies are currently ongoing or recently completed, including, but not limited to, two large-scale long-term safety and efficacy/effectiveness studies of TECFIDERA. Biogen also sponsors various studies targeting specific patient populations, including a registry to examine pregnancy outcomes in women with MS and pediatric patients. We believe this ongoing investment provides important and valuable information to the MS community. While outside of the timeframe of ICER's review, Biogen also additionally provided 27 references published in 2020 and prior to 2018. Of the five studies published in 2020 and submitted to ICER, three evaluated the safety and efficacy of TECFIDERA with nine years' follow-up and real-world safety and effectiveness in Black or African American, and in Hispanic or Latino patients with MS. These studies have contributed to further clarification of TECFIDERA's value proposition and demonstrated Biogen commitment to health equity and to evidence generation that can inform clinical care and assist decision making.	This UPI Report has a specific timeframe.
Bristol Myers Squibb		
1.	New evidence of Orencia's role in precision medicine for RA was provided by the standalone phase IV Early AMPLE trial (NCT02557100) which was not a subgroup analysis of the phase IIIb AMPLE trial (NCT02504268). Early AMPLE trial results were first presented at the annual EULAR conference and the ACR/ARP	We have added a discussion of this trial to the report.

	annual meeting in 2019, with additional results presented at EULAR in 2020. Early AMPLE advanced our understanding of Orencia's effects among patients with early RA who are seropositive for biomarkers associated with rapid disease progression and worse clinical outcomes. The results of Early AMPLE apply to substantial proportions of the RA population (55%-76%) who are seropositive for clinically relevant biomarkers. These patients face an acute need for timely treatment with therapies that have proven efficacy in seropositive populations. Early AMPLE has shed new light on the value of Orencia's unique mechanism of action for patient care, and builds upon a continuum of clinical studies undertaken by BMS, in collaboration with leading clinical experts, to develop an evidence-based foundation for precision medicine in RA. BMS respectfully requests that the Early AMPLE study be included in ICER's assessment of Orencia.	
2.	New evidence of Orencia's safety and tolerability was developed during 2018-2019, based on longer-term follow-up and larger patient populations treated with Orencia, in both clinical trials and real-world care. These studies provide greater confidence in Orencia's safety profile, which represents newly recognized value for patients.	Please see GER 1a, 1b.
Bausch Health		
1.	We assembled the most relevant clinical and health economic evidence, including pivotal studies data and substantial real-world evidence. These studies have helped better define the value of XIFAXAN® (rifaximin) in routine clinical practice settings and provide critical validation for the evidence base for this important therapy. Despite the clear utility of this peer-reviewed work, ICER declined to include them as supportive data.	Please see GER 1a, 1b, 5a.
2.	First, the report arbitrarily excluded key value-based, valid scientific data based on an artificial and rigid standard. Only research published in a narrow date range was considered, an approach that ignores the reality of pharmaceutical research and the development of real-world evidence, in which data sets are often analyzed over time and where publication timelines reflect editorial timelines, and is a poor proxy for when research influences decision making.	We feel that if a manufacturer is planning to raise prices based on new evidence, that evidence should be available to the public.
3.	Second, the report itself promotes subjective value judgments, declaring increases "unsupported" according to a narrow and arbitrary definition that does not consider or define standards for a "supported" increase.	ICER is using GRADE in making judgments about quality of evidence. Judgments about whether benefits are small or substantial are necessarily subjective.

Takeda		
1.	The assessment provided by ICER of the vedolizumab net price increase was incorrect. Takeda has provided the actual data. At the same time, however, several inaccurate assumptions were employed. Over the period 2014 to present, our internal data show that the net price increase of vedolizumab in the US market was less than the overall rate of consumer inflation for the same time frame, which was about 10 percent. For the timeframe of the ICER assessment (2018-2019), the 2.3% net increase was lower than the rate of both the medical consumer price index and overall consumer inflation. Moreover, ICER noted that total market expenditure of vedolizumab increased over this time to highlight the impact of the price increase. However, total expenditure reflects not only price increases but also changes in the market. During this time period, usage of vedolizumab has increased in response to guidelines updates, which now recommend vedolizumab for induction of remission with moderately to severe active UC patients either before or after anti-TNF therapy, including a first-line recommendation over adalimumab in biologic-naïve patients, specifically.	We have corrected the net pricing data.
2.	As part of the assessment, ICER aim to review new evidence for vedolizumab over the prior two years. Whether a price increase is labeled as unsupported hinges on ICER's subjective assessment of the magnitude of clinical effect demonstrated by new evidence. Takeda notes that no transparent criteria are provided regarding differentiation between "small" and "substantial" effects, which dictate whether a price increase is considered supported or unsupported. … Although ICER has acknowledged that the randomized VARSITY trial provided high quality evidence, the UPI report concludes that the magnitude of benefit is small rather than substantial. However, the categorizations of "small" and "substantial" are entirely subjective to ICER. They are not transparent, specific, and replicable, and lack of sensitivity analysis to assess the range effect. Without scientific and rigorous evaluation of clinical benefit, safety profile and patient outcomes evaluation, this conclusion is arbitrary. We strongly urge ICER to leave assessment of magnitude of net health benefit to IBD experts, healthcare providers, and patients. Clinical guidelines from IBD professional societies have been updated to incorporate VARSITY trial data,	Based on additional review, we have concluded that VARSITY provides at least moderate-quality evidence of a new substantial benefit.

	confirming the understood value of this new information within the healthcare community.	
3.	Regarding the uncertainties ICER mentioned, new or updated clinical evidence published during this timeframe which addressed these uncertainties were included among the 13 references Takeda provided to ICER. Of the 13 documents, ICER excluded 12 from the assessment. Among the excluded trials were real-world evidence that demonstrated vedolizumab to have higher rates of clinical, steroid free, and endoscopic healing than comparators. Also excluded were long-term results published from the VICTORY Consortium dataset, the largest US-based real-world registry of IBD patients treated with vedolizumab, which showed that clinical remission at 12-months was achieved in over half of all patients. The prior ICER network meta-analysis only considered RCTs and therefore did not adequately capture long-term real-world outcomes. Long-term studies are particularly effective in identifying durability of treatment. It has been previously demonstrated that early, effective treatments resulting in mucosal healing lowers the risk of colectomy and associated complications, which is value conferred.	Please see GER 2a.
UCB		
1.	Despite UCB's correction, ICER's inclusion of VIMPAT in the 2020 UPI assessment and its preliminary assessment conclusions are based on inaccurate pricing information. To conduct its UPI assessment, ICER relies on pricing information generated by SSR Health to discern individual brand drug net price increases during the assessment period. In fact, the entire UPI assessment process—from inclusion selection to the ultimate determination of "price justification"— hinges on this SSR Health data. Therefore, it stands to reason that the accuracy of this data is essential to the validity of ICER's conclusions. According to SSR Health, as described by ICER in its preliminary assessment of VIMPAT: "Over the 12-month (four quarters) period for which price changes were assessed, lacosamide's wholesale acquisition cost (WAC) increased by 7%, while its net price increased by 10%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $104 million." ICER's data is inaccurate. UCB provided ICER with this correction in a letter dated July 17, 2020 [see Appendix B]. Despite this correction, ICER has continued to use a net price increase figure that is almost double the actual	We have corrected the net pricing data.

	amount, without acknowledgement or explanation of the discrepancy.	
2.	Despite UCB's submission of significant new clinical evidence in support of VIMPAT's actual net price increase, ICER arbitrarily excluded every reference provided based on inconsistent and nontransparent interpretations of its inclusion criteria. Based on this protocol, UCB submitted 25 references to be considered as new clinical evidence supporting VIMPAT's actual net price increase. ICER excluded each and every reference from consideration. Unsurprisingly, this failure to consider the clinical evidence resulted in ICER making a preliminary assessment that VIMPAT had a (inaccurate) price increase unsupported by new clinical evidence. Of the 25 references ICER excluded, eight were arbitrarily excluded based on ICER's explanation that "study was published outside of the timeframe for our review," despite the fact that they produced new evidence during the 2018-2019 review period. However, nowhere in ICER's UPI Assessment protocols does it say that new clinical evidence must be published during the timeframe of the review. The protocol simply refers to "new information." … For these reasons, ICER's decision to exclude the bulk of the new clinical evidence for VIMPAT—most of which was generated, but not yet published during the timeframe for review—is an utterly arbitrary and inconsistent interpretation of its very vague protocols.	We believe that information should be publicly available if a manufacturer is planning to substantially increase the price of therapies responsible for the largest budget impact in the US.

Appendix L. Manufacturer Comments

Full-text manufacturer comments on our preliminary assessments are displayed on the following pages.

November 24, 2020

AbbVie supports an evidence-based value assessment paradigm that reflects the unique and diverse criteria of stakeholders impacted by the assessment and those making healthcare decisions, and that preserves shared decision making between patients and their healthcare providers.

Since its FDA approval in 2002, HUMIRA has helped transform care for 1,000,000+ patients who suffer from the effects of their immune-mediated diseases. AbbVie's dedicated investment in the research and development around HUMIRA has resulted in a notable therapeutic option available to a diverse set of patients suffering from 10 different immune-mediated diseases in the U.S., including orphan, or rare disease, conditions. In addition, our investment in research and with the patient experience in mind has resulted in the development of HUMIRA's new citrate-free formulation and its benefit including less pain following an injection, a thinner needle and the delivery of the same amount of active ingredient but in less injectable volume. Our ongoing research with respect to HUMIRA into a variety of approaches enables us to remain focused on helping patients achieve their treatment goals.

AbbVie remains focused on discovering and developing transformative therapies that deliver compelling patient benefits, differentiated clinical performance and clear economic value, while purposefully advancing the standard of care. As such, AbbVie appreciates the opportunity to comment on ICER's Unsupported Price Increase (UPI) Preliminary Assessment of Humira (adalimumab).

AbbVie's Position on ICER Unsupported Price Increase Assessment

AbbVie respectfully disagrees with the conclusions ICER reached regarding HUMIRA in its Unsupported Price Increase (UPI) Assessment and highlights these notable limitations to ICER's review process:

- AbbVie Submitted Evidence Should Be Within Scope of ICER Review. As a company committed to ongoing research and development, AbbVie believes in the growing body of clinical, economic and humanistic evidence and that every piece of evidence, whether from randomized studies, real-world evidence, long-term follow-up, or economic studies advances the clinical community's understanding of both HUMIRA and the diseases it treats. It is in this spirit that we submitted 58 references to publications over the prior two years (beginning of 2018 through the end of 2019) for ICER's consideration. By excluding high-quality evidence from its assessment ICER cannot assess the totality of research available to demonstrate the value of a product to patients, physicians, and payers. We believe these additional publications contribute to the body of evidence supporting the net health benefit of HUMIRA that should be considered.

- UPI Assessment Fails to Account for Rare Conditions and Underserved Populations. In limiting the assessment to indications representing greater than 10 percent use, ICER excluded HUMIRA's clinical and economic evidence in smaller patient populations, including rare conditions and pediatric populations that reflect our commitment to innovation and improvement in net health benefit to underserved populations with high unmet needs.

- UPI Assessment Does Not Factor in AbbVie's Dedication to Patient Access and Continued Investment in Patient Access and Patient-Centric Programs. The assessment does not appropriately account for AbbVie's dedication to patient access and continued investment and innovation in HUMIRA through the development of patient-centric programs.

abbvie

AbbVie Submitted Evidence Demonstrating Clinical, Economic and Humanistic Benefit of HUMIRA Should Be Considered

To assist ICER with this systematic review, AbbVie provided 58 scientific publications that support HUMIRA's safety, clinical effectiveness, and economic value. ICER determined that none of the evidence fully met the review process criteria. It is AbbVie's position that in rejecting all of AbbVie's submitted research from consideration, ICER has excluded high-quality evidence of the added net health benefit of HUMIRA.

The following examples highlight some of the high-quality evidence of added net health benefit that AbbVie submitted to ICER and believes merit consideration under the UPI protocol:

Real-World Evidence:

- *Systematic review of the real-world evidence of adalimumab safety in psoriasis registries. Strober B, et al. J Eur Acad Dermatol Venereol 2018;32:2126-2133.*
- *Long-term, Real-world Safety of Adalimumab in Rheumatoid Arthritis: Analysis of a Prospective US-Based Registry. Harrold LR, et al. J Rheumatol 2020 Jul 1;47(7):959–967.*

Long-Term Follow-Up from Clinical Trials:

- *Clinical benefit of long-term adalimumab treatment in patients with Crohn's disease following loss of response or intolerance to infliximab: 96 week efficacy data from GAIN/ADHERE trials. Panaccione R, Sandborn WJ, D'Haens G, et al. J Crohn Colitis. 2018;12(8):930 938.*

Economic and Humanistic Studies:

- *Retrospective Analysis of the Impact of Adalimumab Initiation on Corticosteroid Utilization and Medical Costs Among Biologic-Naïve Patients with Rheumatoid Arthritis. Spivey CA, et al. Rheumatol Ther 2020; 7(1):133–147.*
- *Network meta-analysis and cost per responder of targeted immunomodulators in the treatment of active psoriatic arthritis. Strand V, Elaine Husni M, Betts KA, et al. BMC Rheumatology. 2018;2(1).*

UPI Assessment Fails to Account for Rare Conditions and Vulnerable Populations

AbbVie continues to identify ways in which HUMIRA addresses important unmet medical needs. In 2019, AbbVie invested $5 billion in research and development. With respect to HUMIRA specifically, AbbVie's research has resulted in an important therapeutic option for patients suffering from 10 different diseases in the U.S., including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), adult Crohn's disease (CD), pediatric Crohn's disease, ulcerative colitis (UC), plaque psoriasis (Ps), adult and adolescent hidradenitis suppurativa (HS), and adult and pediatric non-infectious uveitis (UV). And as we advance research, we aim to bring to life our vision of reducing the burden for all those touched by immune-mediated diseases.

In limiting the UPI assessment to only those indications representing greater than 10 percent of use, ICER excluded evaluation of clinical, economic and/or humanistic evidence for rare conditions and pediatric indications. AbbVie disagrees with a methodology that discounts the investment in improving clinical practice and advancing standard of care and value provided to pediatric patients and patients suffering from rare diseases, simply because such patients are fewer in number. Just as FDA incentivizes the development of evidence regarding the treatment of orphan and rare diseases, ICER should acknowledge and consider in its assessment the value of investing in smaller, yet high burden, disease areas.

- *Achieving hidradenitis suppurativa response score is associated with significant improvement in clinical and patient-reported outcomes: Post hoc analysis of pooled data from PIONEER I and II. Kimball AB, et al. Acta Derm Venereol 2018;98:932–937.*

UPI Assessment Does Not Factor in AbbVie's Dedication to Patient Access and Continued Investment in Patient Access and Patient-Centric Programs.

While ICER's UPI Assessment does not directly address patient access, AbbVie is committed to ensuring that the safe and effective use of HUMIRA is made available to indicated patients and with appropriate product support.

In 2020, in excess of 95% of national commercial and Medicare Part D plan patients have coverage for HUMIRA as a preferred, first-line TIM and AbbVie makes available a savings card to eligible commercial patients that may reduce their out of pocket cost to as little as $5 per month.

Beyond our dedication to patient access, AbbVie continues to invest in patient-centric programs, including the development of its strong relationship with advocacy groups and disease state educational programming and its patient support program for HUMIRA, known as HUMIRA Complete in the U.S., which delivers personalized product support through a combination of personal interactions, digital solutions, and sophisticated data management. A recent study evaluating the impact of HUMIRA Complete demonstrated that enrolled patients had all-cause medical costs that were significantly lower than patients who were not enrolled in a patient support program.

- *Patient Support Program Increased Medication Adherence with Lower Total Health Care Costs Despite Increased Drug Spending. Brixner D, et al. J Manag Care Spec Pharm 2019;25(7):770–779.*

AbbVie sponsored or provided support for over 20 registries (e.g. PYRAMID, CORRONA, ESPRIT, LEGACY) including registries for nine immune-mediated diseases. On an annual basis, our financial support of these immunology registries exceeds $20 million. This investment helps the scientific community gain a better understanding of these chronic immune-mediated diseases, which may lead to improvements in the quality of care provided to the millions of patients afflicted by these immune-mediated diseases. Examples of important and high-quality evidence coming from registries include:

- *Loftus, EV et al. Adalimumab Effectiveness Up to Six Years in Adalimumab-naïve Patients with Crohn's Disease: Results of the PYRAMID Registry Inflammatory Bowel Diseases, izz008, doi.org/10.1093/ibd/izz008.*
- *Pappas, DA et al. Long-Term Effectiveness of Adalimumab in Patients with Rheumatoid Arthritis: An Observational Analysis from the CORRONA Rheumatoid Arthritis Registry. Rheumatol Ther, 2017 ISSN: 2198-6576, 2198-6584.*

In conclusion, a reliable and complete assessment of the value of HUMIRA should look holistically at AbbVie's investment in HUMIRA, from clinical and economic evidence to patient experiences. AbbVie remains focused on discovering and developing transformative therapies that deliver compelling patient benefits, safety vigilance, differentiated clinical performance and clear economic value, while purposefully advancing the standard of care. AbbVie hopes that the concerns it has raised brings stakeholders together to find sustainable, system-wide solutions that lower costs while protecting scientific innovation and access to breakthrough treatments.

Amgen appreciates the opportunity to respond to ICER's *Unsupported Price Increase Assessment: Preliminary Assessment of Enbrel*® shared on October 27, 2020. ICER did not identify Enbrel in its initial protocol-based search of 2020 UPI drugs with price increases; however, Enbrel was later included based on subjective criteria (*i.e.,* public input). Amgen is committed to the discovery and development of new medicines and enabling access for patients. While Amgen has invested in studying Enbrel® (etanercept) for additional indications and to introduce new, more patient-friendly formulations and administration methods, the landscape is particularly complex.[1] Enbrel is in a highly competitive marketplace that includes approximately 20 products that compete for formulary position to enable access. Due to the way secondary entities structure contracts, increases in list prices may increase total rebates to these entities. In this environment, Amgen has increased list prices in response to competitor list price increases to remain available as a choice on formularies. Such measures are required to maintain Amgen's commitment that every patient who needs our medicine has meaningful access to our products. Given this complexity, ICER's published UPI methodology as designed, has intrinsic limitations in its ability to tie to these dynamics, which could dramatically impact patient access to medicines. Notwithstanding these considerations, when applying ICER's published methodology and criteria, Enbrel is not qualified as having an unsupported price increase.

The SEAM-PsA trial is meaningful new evidence supportive of Enbrel's price increase. Of the 17 references Amgen submitted as new clinical information within ICER's timeframe of review (January 1, 2018 to December 31, 2019), ICER excluded all of these on the basis that none met its inclusion criteria of new information on benefits and/or harms within the indications that account for greater than 10% of use. In this letter, we outline why the information from the SEAM-PsA trial provides new data, not previously known, and positively contributed to the value and evidence in supporting patient and physician decision-making in optimizing treatment. We would request that ICER looks more closely at the trials cited as evidence that the SEAM-PsA trial findings were 'known'. Given the timing of SEAM-PsA, and underpinned by statements in the 2018 ACR/NPF guidelines,[2] this is not the case. The SEAM-PsA trial as ICER notes is a "very well-conducted" RCT. This supports Enbrel's price increase using ICER's current UPI methodology. Further, it is crucial that ICER includes aspects of value important to patients, such as lower pain formulations, and factors involving the complex competitive dynamic. Amgen supports ICER's position that poorly designed trials or evidence should not be used to support a price increase, which is not the case with SEAM-PsA.

In short, based on ICER's draft evidence review of Enbrel for its UPI assessment, we recommend:

- **ICER should consider the SEAM-PsA trial as meaningful new evidence and recalibrate its assessment of these data as supportive of Enbrel's price increase.**
  - **Prior studies referenced by ICER [CHAMPION, RESTORE1, RESPOND] should be disregarded**. These studies either utilized incomparable endpoints [*i.e.,* Psoriasis Area and Severity Index (PASI) versus American College of Rheumatology (ACR) 20] or were in combination with methotrexate (MTX) versus monotherapy and involved different anti-TNF therapies.

Below we expand upon these points in more detail.

RECOMMENDATIONS & EVIDENCE INTERPRETATION

- **ICER should consider the SEAM-PsA trial as meaningful new evidence and recalibrate its assessment of these data as supportive of Enbrel's price increase.**

The SEAM-PsA[3] randomized clinical trial (which was published after the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) Guideline for the Treatment of Psoriatic Arthritis)[4] qualifies as *new evidence.* ICER's 2019 UPI Report determined that two products, Genvoya® and Revlimid® did not have unsupported price increases: this was based on clinical evidence for these two products that is no different from the clinical evidence for Enbrel. The SEAM-PsA trial provides improved clinical evidence that shifted the evidence base and the understanding of the magnitude of net benefit, which was previously considered "*Low- to very low-quality evidence*" in the 2018 ACR/NSF guideline which was published while the SEAM-PsA trial was on-going.

Prior studies referenced by ICER as justification to exclude SEAM-PsA [CHAMPION, RESTORE1, RESPOND] should be disregarded. These studies either utilized incomparable endpoints [*i.e.*, PASI versus ACR20] or were in combination with methotrexate (MTX) versus monotherapy and involved different anti-TNF therapies.

- **ACR20 is a core outcome measure that is of direct importance to patients that was excluded in CHAMPION and RESTORE1.** These trials did *not* measure the devastating inflammation, pain and disability that psoriatic arthritis patients face with this disease, but rather measured the impact on skin lesions (erythema, thickness, and scaling) of psoriatic plaques. The **CHAMPION[5]** trial was a randomized, double-blind, double-dummy, placebo-controlled study to compare adalimumab (another anti-TNF) with oral methotrexate and with placebo in patients with moderate to severe psoriasis. It was not a trial of psoriatic arthritis, although as expected, between 17 to 21% of subjects also suffered from psoriatic arthritis [Table 1]. Similarly, the **RESTORE1[6]** trial compared the patient population in an open-label trial in methotrexate-naïve patients with moderate to severe plaque psoriasis and 24% of the subjects suffered from psoriatic arthritis. The **CHAMPION[7] and RESTORE1[8] trials** focused on [PASI] and *not* the $\geq$ 20% improvement in ACR, which is the widely accepted endpoint for assessing arthritic and systemic disease activity for PsA. PASI[9,10] is a quantitative rating score for measuring the severity of psoriatic lesions while ACR20 is used to assess and establish the improvement in tender or swollen joint counts and global or patient assessment of pain or disability/functionality.[11]
- **The RESPOND study[12] did not establish anti-TNFs as a monotherapy for use in treatment naïve PsA patients.** The third trial (RESPOND) ICER cites to exclude the SEAM-PsA trial, used a different drug (infliximab) in combination with methotrexate (MTX), and did not incorporate a TNFi-monotherapy arm. The study was open-label in design and involved a different drug (infliximab). Furthermore, the trial only compared methotrexate with infliximab *in combination* with methotrexate. In contrast, the SEAM-PsA trial was designed with three arms: a MTX monotherapy arm, an Enbrel monotherapy arm, and a combination therapy of MTX and Enbrel arm. The trial demonstrated that Enbrel, used as monotherapy (and in combination with MTX), was superior to MTX alone using ACR20 and MDA (Minimal

Disease Activity). In general, combining MTX and Enbrel showed similar efficacy to Enbrel alone in these disease outcomes thus showing that MTX may not contribute meaningfully to treatment of this population of PsA patients. A survey conducted in 2019 of 121 patients (88.4% rheumatoid arthritis, 22.3% PsA, not mutually exclusive) showed that a majority of patients experience side effects such as fatigue, nausea and brain fog attributed to MTX.[13] These results provide important information for patients and their physicians to help optimize the treatment regimen with Enbrel and reduce the treatment burden associated with combination therapy.

ICER's selected trials also involved different anti-TNFs with key immunogenicity differences such as the development of anti-drug antibodies (ADAs). ADA formation leads to loss of efficacy and is associated with lower ACR20 response, where drugs such as infliximab and adalimumab result in therapeutic failure due to ADAs in various autoimmune diseases like rheumatoid arthritis,[14,15] spondyloarthritis[16] and Crohn's disease.[17] The RESTORE1/RESPOND and CHAMPION studies involved infliximab and adalimumab, respectively. Studies have shown that ADA development has been associated with decreased clinical efficacy in these two monoclonal antibody TNF inhibitors: (*e.g.*, antibodies against infliximab were correlated with decreased clinical response in five studies, and anti-adalimumab antibodies corresponded with lower clinical efficacy in 3 out of 5 studies).[18,19] In contrast, Enbrel studies have shown minimal development of ADAs[20] and furthermore, the ADAs against Enbrel were non-neutralizing and not associated with any apparent effects on clinical response.[21] Further expansion on the immunogenicity differences across the anti-TNFs over various autoimmune diseases is available in Table 2 in the Appendix.

Conclusion

Based on ICER's published methodology and criteria, Enbrel did not have an unsupported price increase. We have also provided strong evidence that there were no head-to-head to studies published before January 2018 that showed that TNF inhibitors had superior efficacy (*i.e.*, specifically $\geq$ 20 improvement in ACR) as a monotherapy in treatment-naïve PsA patients. Amgen urges ICER to closely review the timing of the SEAM-PsA trial since the study was "on-going" at the time the ACR/NPF guidelines were published, and were noted as "will inform treatment decisions" in those guidelines. Amgen continues to invest in high quality randomized controlled study evidence, real-world evidence as well as innovation on outcomes important to patients. Psoriatic arthritis is a very serious chronic disease and Amgen believes it is important to provide access for both physician and patient choice in selecting the optimal clinical treatment. Completed in 2019, SEAM-PsA included nearly 900 patients and as ICER noted, this trial was a well-conducted randomized controlled trial. In this document, we have provided additional information that supports that this trial was the first head-to-head trial involving a TNF inhibitor monotherapy in PsA treatment naïve patients and kindly request ICER reconsider the inclusion of this particular study as supportive of a price increase.

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APPENDIX

Table 1 expands on the quality of the evidence cited by ACR/NPF. In this table, it can be seen that the references do not support the same conclusions from the SEAM-PsA trial and hence, the conclusions from SEAM-PsA trial were not "confirmatory of prior beliefs".

Table 1: ACR list of references: The trials referenced in the ACR/NPF guidelines were not sufficient to change usage in treatment naïve PsA patients.

ICER ref. #	Year	Study	URL	Why this study as referenced by the ACR Guidelines is not sufficient to support the same conclusions from the SEAM-PsA trial (and therefore not previously known information)
53	2012	**Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study**	Link	• **Not a monotherapy:** Infliximab plus methotrexate with methotrexate alone in methotrexate-naive patients with active psoriatic arthritis (PsA) • **Weaker study design:** Open-label in design • **Different Drug:** Infliximab
54	2007	**The comparative effectiveness of anti- TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicenter study**	Link	• **Weaker study design:** Longitudinal, observational multicenter study • **Not a monotherapy:** 146 patients received TNF-blocking agents (44 infliximab, 83 etanercept and 19 adalimumab, of these 75%, 60% and 79%, respectively, with concomitant MTX (mean (SD) dose 12.5 (4.7) mg weekly)). • **Patient population differences:** A total of 108 (74%) of the patients in the anti-TNF group had previously used MTX, and 39 of these patients were previously included in the MTX group.
55	2014	**Tumor necrosis factor α blockers are more effective than methotrexate in the inhibition of radiographic joint damage progression among patients with psoriatic arthritis**	Link	• **Weaker study design:** A cohort analysis of patients followed prospectively from 1978 to 2010 at the University of Toronto PsA clinic • **Not a monotherapy:** Sixteen out of 65 (24.6%) of the patients in the TNFα blockers treatment group used concomitant methotrexate at baseline
56	2011	**Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1)**	Link	• **Different drug:** Infliximab • **Patient population (different disease):** 653 patients were studied with plaque psoriasis, although 154 of those had psoriatic arthritis • **Weaker study design:** Open-label
57	2008	**Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION).**	Link	• **Different drug:** adalimumab • **Patient population (different disease):** 271 plaque psoriasis patients although 20.8%, 17.3%, and 21.3% of those patients (placebo, methotrexate, adalimumab group, respectively) had psoriatic arthritis

Table 1 (*continued*)

ICER ref. #	Year	Study	URL	Why this study as referenced by the ACR Guidelines is not sufficient to support the same conclusions from the SEAM-PsA trial (and therefore not previously known information)
58	2012	**A randomized placebo-controlled trial of methotrexate in psoriatic arthritis**	Link	• **Patient population differences:** No Anti-TNF, only MTX or placebo • **Different Drug:** MTX
59	1995	**Sulfasalazine therapy for psoriatic arthritis: a double blind, placebo controlled trial.**	Link	• **Patient population differences:** Only sulfasalazine or placebo, no mention of MTX • **Different Drug:** Sulfasalazine
60	1996	**Sulphasalazine in psoriatic arthritis: a randomized, multicenter, placebo-controlled study.**	Link	• **Patient population differences:** Only sulfasalazine or placebo, no mention of MTX • **Different Drug:** Sulfasalazine
61	1990	**Sulfasalazine in psoriatic arthritis: a double- blind placebo- controlled study.**	Link	• **Patient population differences:** Only sulfasalazine or placebo, no mention of MTX • **Different Drug:** Sulfasalazine
62	2005	**Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. (MEASE)**	Link	• **Different Drug:** Adalimumab • **Patient population differences:** Adalimumab vs placebo • **Not a monotherapy:** MTX use was allowed during the study only if it had been taken for at least 3 months previously, with the dosage stable for at least 4 weeks prior to the baseline visit.(Placebo (MTX usage at baseline): 50%, adalimumamb (MTX usage at baseline): 51%)
63	2007	**Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial**	Link	• **Different Drug:** Adalimumab • **Patient population differences:** Adalimumab vs placebo • **Not a monotherapy:** Before randomization, patients were stratified according to methotrexate (MTX) use (yes/no) and degree of psoriasis involvement at baseline
64	2004	**Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression (MEASE)**	Link	• **Patient population differences:** Etanercept vs placebo (Not vs. MTX) • **Not a monotherapy:** Concomitant methotrexate therapy, which had been stable for 2 months, could be continued at a stable dosage of ≤25 mg/week. (41% placebo patients were o MTX and 42% of Etanercept patients were on MTX)
65	2010	**Patient- reported outcomes in a randomized trial of etanercept in psoriatic arthritis. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis (MEASE)**	Link	• **Patient population differences:** Etanercept vs placebo (Not MTX) • **Not a monotherapy:** Patients receiving methotrexate who were going to continue methotrexate were randomized separately from those who were not receiving methotrexate
66	2000	**Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial (MEASE)**	Link	• **Patient population differences:** Etanercept vs placebo (Not MTX)

Table 2: Immunogenicity Differences in the Anti-TNFs

The below table expands on the immunogenicity differences across different anti-TNFs across various autoimmune diseases.

Anti-TNFs	Immunogenicity Differences - RA	Immunogenicity Differences - Other Autoimmune Diseases
Infliximab	ADA-positive patients receiving MTX had lower antibody levels than those not receiving MTX.[22] A Spanish study observed that although not associated with significant lower proportions of ADAs with concomitant MTX usage, receiving both infliximab and MTX tended toward lower anti-infliximab antibodies and longer drug survival.[23]	**PsA** • IMPACT2 trial: 3.6% of patients receiving MTX + infliximab were positive for antibodies to infliximab, while 26.1% not receiving infliximab monotherapy tested positive for anti-infliximab antibodies.[24] **Ankylosing Spondylitis** • Significantly higher AS disease activity score was associated with patients with ADAs to infliximab than those without the antibodies.[25] **Crohn's disease** • Corticosteroids (intravenous hydrocortisone pre-treatment) associated with reducing anti-infliximab antibody concentrations, but not their formation.[26]
Adalimumab	ADAs were associated with reduced improvement in disease activity and concomitant MTX usage was related to lower rate of ADA development than adalimumab monotherapy.[27] Immunogenicity increased when switching from infliximab to adalimumab: patients who switched from infliximab to adalimumab after initially developing anti-infliximab antibodies, developed ADAs more often than anti-TNF naïve patients.[28] Clear dose dependent relationship with MTX and reduction in ADA formation: Increase in MTX was inversely proportional to % of patients developing ADAs.[29]	**Psoriasis** • Trend observed where MTX use reduced immunogenicity to anti-TNFs.[30,31]

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December 16, 2020

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
2 Liberty Square, 9th Floor
Boston, MA 02109

RE: ICER's Updated UPI Preliminary Assessment of XTANDI® (enzalutamide)

Dr. Pearson:

We appreciate the opportunity to comment on ICER's updated Unsupported Price Increase (UPI) Preliminary Assessment of XTANDI and disagree with XTANDI's inclusion in the 2020 UPI Report.

Astellas continues to agree with the Preliminary Assessment's conclusion that price changes in XTANDI were accompanied by new clinical evidence during the period of analysis. We also agree that "new evidence from the PROSPER trial, the ARCHES trial, and the ENZAMET trial provide high certainty of a substantial benefit for enzalutamide compared with what was previously known." These examples demonstrate the substantial benefit that we have delivered to patients through reinvestment of revenue into continued research and development. In these three trials alone, Astellas and our partner Pfizer will have invested more than $370 million in R&D related to XTANDI over a nine-year period. This investment is in addition to more than $1 billion in historical R&D investment to support the medicine's development and approval.

ICER initially estimated a net price increase for XTANDI of 15.9% and a corresponding estimated spend increase of $230 million. Early on and on several occasions through the assessment period, Astellas provided corrected data to ICER on net price increase of 2.5% during the period between 2018 and 2019. It was only after the final manufacturer input period that ICER requested the additional data point for increase in drug spending which Astellas provided (estimated $37 million). ICER subsequently adjusted its calculations and confirmed that XTANDI moved much further down in the list of drugs under consideration for the UPI Report, to no longer be in the top 10. However, ICER has continued to include XTANDI in the assessment even after acknowledging that XTANDI does not meet the criteria established in ICER's 2020 UPI Protocol.

ICER's 2020 UPI Protocol provided an established and detailed process for determining which drug products would be included in the UPI Report. The 2020 Protocol provided that, "[a]fter resolution of any concerns about estimates, the top 10 drugs remaining on the list will constitute the final list of drugs for which the evidence review will be undertaken." While Astellas commends ICER's correction of its initial net price increase and spend estimates for XTANDI, we disagree with XTANDI's inclusion in the 2020 UPI Report (which is contrary to ICER's 2020 UPI Protocol).

We urge ICER to adhere to its protocol and exclude XTANDI from the UPI Report.

Sincerely,

Shontelle Dodson
Senior Vice President, Health Systems
Astellas Pharma US, Inc.

Astellas Pharma US, Inc.
1 Astellas Way, Northbrook, IL 60062

November 24, 2020

RE: ICER's Unsupported Price Increase Assessment for dimethyl fumarate (TECFIDERA®)

Biogen appreciates the opportunity to comment on ICER's draft Unsupported Price Increase Assessment for TECFIDERA. In this assessment, ICER aims to review new evidence for TECFIDERA over a 24-month period (January 1, 2018 – December 31, 2019) on efficacy, safety, economic outcomes, and other potential justifications to evaluate the increase in price from 2018 to 2019.

Biogen Disagrees with ICER's Exclusion of 17 References Published in 2018 – 2019 Provided by Biogen

Biogen provided 17 references published in 2018 and 2019. ICER excluded all 17 of these references in their assessment. Additionally, ICER did not conduct a search for additional new evidence.

Eight of the 17 studies published in 2018 - 2019 were comparative effectiveness studies that consistently demonstrate that TECFIDERA has superior clinical outcomes compared to glatiramer acetate, teriflunomide, and interferons and has similar outcomes to fingolimod.[1-8] Results from various other prospective, observational studies submitted also demonstrate TECFIDERA's significant impact on quality of life, healthcare resource utilization, and other patient-reported outcomes (PROs) for patients with MS.[5,9-10] Biogen respectfully disagrees with the exclusion for these studies as they provide important new and confirmatory clinical information on TECFIDERA.

While observational studies do not always merit a similar quality grade to that of RCTs, it is disappointing that all observational studies in the TECFIDERA assessment have been excluded in this report as they can inform clinical care. Excluding these studies[1-17] dismisses a large volume of previously unpublished, peer-reviewed, scientific evidence, often for different patient subgroups, follow-up duration, data sources, and / or countries, consistently showing that TECFIDERA has superior outcomes as compared to teriflunomide, glatiramer acetate, and interferons and has similar outcomes as compared to fingolimod.

ICER's reliance on the GRADE method for evaluation of evidence is inconsistent with the evolution of key stakeholders' sources of evidence and increasing emphasis on use of real-world research. Furthermore, payers, clinicians, and regulators increasingly look to well-conducted observational studies to address existing evidence gaps, such as efficacy in populations not previously studied in RCTs due to rigid inclusion/exclusion criteria.[18-21]

Biogen strongly recommends that ICER re-evaluate the observational studies supporting the benefits of TECFIDERA and consider approaches for assessing the value of real-world,

observational research, which is an important element to inform clinical decision-making and patient care. Reports such as these have the potential to devalue or reduce incentives for manufacturers to generate more evidence on the value of therapies, thus limiting the evidence available to improve decision-making.

Biogen's Commitment to Invest in Evidence Generation, Including Long-Term Efficacy and Safety Follow-Up and Multiple MS Patient Types

Since the TECFIDERA launch, Biogen has invested significantly in studies that further clarify and demonstrate TECFIDERA's value proposition to better assist payers and clinicians with their decision-making regarding treatment of relapsing MS.

Multiple prospective, observational, or interventional studies are currently ongoing or recently completed, including, but not limited to, 2 large-scale long-term safety and efficacy/effectiveness studies of TECFIDERA.[22-23] Biogen also sponsors various studies targeting specific patient populations, including a registry to examine pregnancy outcomes in women with MS[24] and pediatric patients.[25] We believe this ongoing investment provides important and valuable information to the MS community.

While outside of the timeframe of ICER's review, Biogen also additionally provided 27 references published in 2020 and prior to 2018. Of the 5 studies published in 2020 and submitted to ICER, 3 evaluated the safety and efficacy of TECFIDERA with 9 years' follow-up[26] and real-world safety and effectiveness in Black or African American,[27] and in Hispanic or Latino patients with MS.[28] These studies have contributed to further clarification of TECFIDERA's value proposition and demonstrated Biogen commitment to health equity and to evidence generation that can inform clinical care and assist decision making.

As a leader in MS, Biogen understands the importance of research to generate long-term follow-up on the safety and efficacy/effectiveness of TECFIDERA as well as addressing evidence gaps on multiple MS patient types. We respectfully disagree with the assessment on TECFIDERA and believe that this evaluation does not represent the value proposition of TECFIDERA.

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Bristol Myers Squibb™

November 23, 2020

RE: Preliminary Report, ICER Unsupported Price Increase Assessment 2020

As a global biopharma company whose mission is firmly focused on discovering, developing, and delivering innovative medicines for patients with serious diseases, we have divergent views from ICER's unsupported price increase assessment of Orencia® (abatacept), and appreciate this opportunity to comment.

Orencia represents Bristol Myers Squibb's (BMS's) long-standing commitment to developing innovative medicines that address unmet needs; the medicine is a safe, effective, disease-modifying treatment for rheumatoid arthritis (RA), psoriatic arthritis (PsA), and polyarticular juvenile idiopathic arthritis (pJIA). Importantly, Orencia provides a unique mechanism of action as a selective T cell costimulation modulator[1] – making it a critically important option for patients who are unlikely to benefit from or tolerate other treatments.

At BMS, we take great care to price our medicines based on the value they deliver, the scientific innovation they represent, economic factors that impact healthcare systems' capacity to provide appropriate, rapid, and sustainable access to patients, and the investment necessary to develop them. ICER's assessment of Orencia was, in our view, limited by criteria that disregarded these broader dynamics and their impacts on price. In addition, even within the specified criteria, important evidence of Orencia's value was, from our perspective, unduly excluded. To better understand the rationale for inclusion or exclusion of evidence in ICER's assessment, BMS requested a meeting with ICER. We appreciated ICER's openness to discussion. Following our meeting on 11/5/2020, we would like to highlight the novelty and importance of two collections of evidence, selected from the larger body of evidence submitted in our initial response:

- New evidence of Orencia's role in precision medicine for RA was provided by the standalone phase IV Early AMPLE trial (NCT02557100) which was not a subgroup analysis of the phase IIIb AMPLE trial (NCT02504268). Early AMPLE trial results were first presented at the annual EULAR conference and the ACR/ARP annual meeting in 2019,[2,3] with additional results presented at EULAR in 2020.[4,5] Early AMPLE advanced our understanding of Orencia's effects among patients with early RA who are seropositive for biomarkers associated with rapid disease progression and worse clinical outcomes. The results of Early AMPLE apply to substantial proportions of the RA population (55%-76%) who are seropositive for clinically relevant biomarkers.[6,7] These patients face an acute need for timely treatment with therapies that have proven efficacy in seropositive populations. Early AMPLE has shed new light on the value of Orencia's unique mechanism of action for patient care, and builds upon a continuum of clinical studies undertaken by BMS, in collaboration with leading clinical experts, to develop an evidence-based foundation for precision medicine in RA. BMS respectfully requests that the Early AMPLE study be included in ICER's assessment of Orencia.

- New evidence of Orencia's safety and tolerability was developed during 2018-2019, based on longer-term follow-up and larger patient populations treated with Orencia, in

both clinical trials and real-world care. These studies provide greater confidence in Orencia's safety profile, which represents newly-recognized value for patients. [8-14]

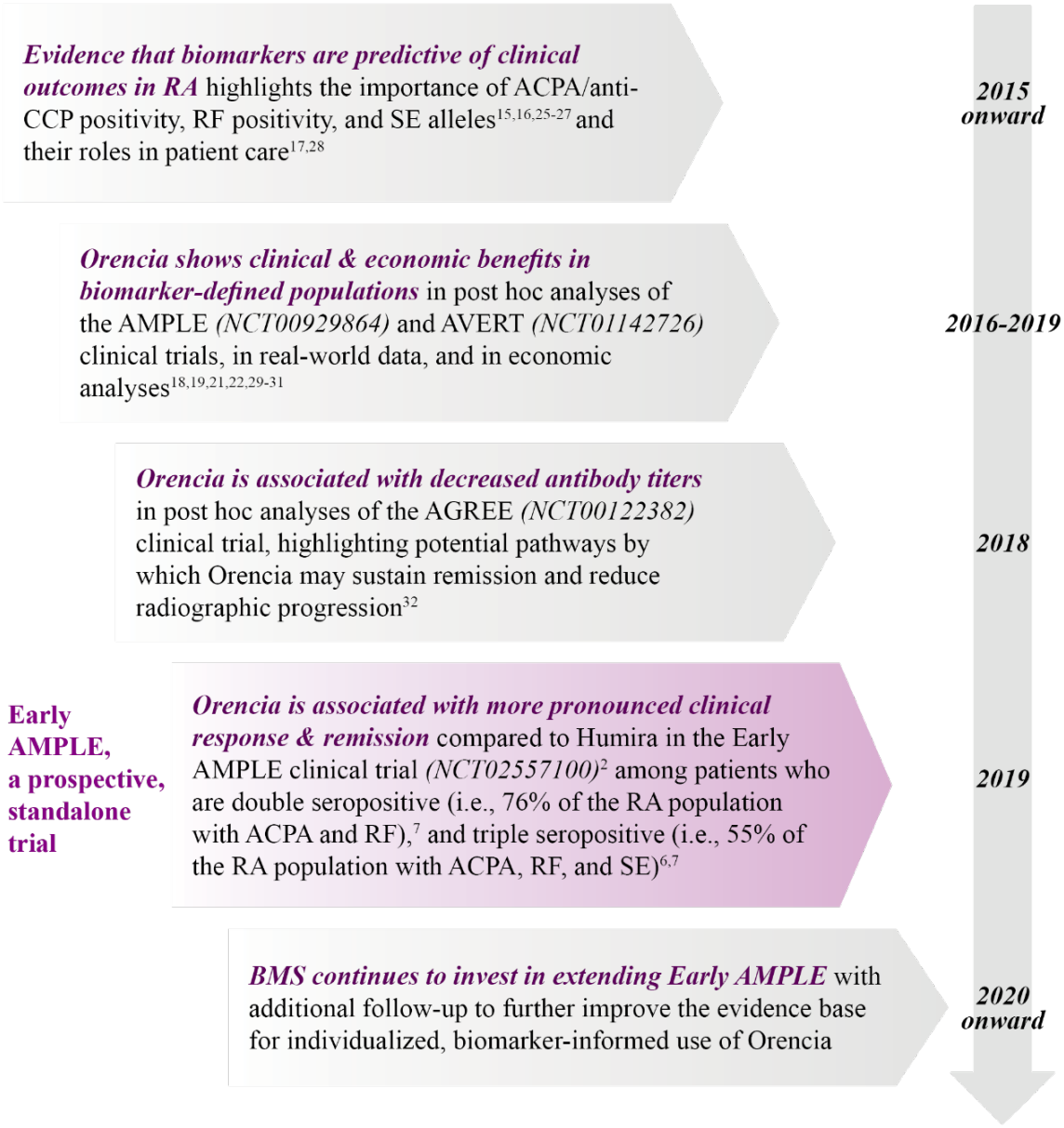
The following sections further describe these sources of evidence, and BMS's long-standing commitment to innovation with Orencia.

Precision medicine with Orencia

People living with seropositive RA experience more rapid disease progression and onset of disability than others. [15,16] There is a need to identify these cases early and match them to treatments that have demonstrated benefits specifically for people with seropositive disease. Precision medicine, with individualized treatment informed by prognostic biomarkers, is emerging as an important component of the treat-to-target paradigm in RA.[17] In addition to improved clinical outcomes, precision medicine for RA can improve the cost-effectiveness of care.[18] Achieving the full promise of precision medicine in RA, however, will require long-term investment in developing the evidence necessary to inform individualized care. BMS has been a leader in bringing precision medicine to RA, and has invested in an extensive program of collaborative research to inform Orencia's role in biomarker-defined populations.

Orencia's efficacy has been demonstrated among patients with early RA and biomarkers associated with faster progression, including seropositivity for anti-citrullinated protein antibodies (ACPA) or its surrogate, anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), and shared epitope (SE) in analyses of multiple clinical trials or real-world studies (see **Figure 1** below). [2,10,15,19-24] Building on this cumulative evidence, the recent biomarker-driven Early AMPLE trial provided a significant step forward in understanding differential response to biologics in seropositive early RA. Early AMPLE prospectively explored changes in the immune profile of early RA patients with ACPA and RF seropositivity. Patients treated with Orencia + MTX had numerically improved responses compared with Humira + MTX, with more pronounced treatment differences in the SE+ population.[2] BMS has continued to invest in this study with protocol amendments to further represent early RA patients. Additional follow-up was conducted to further build the evidence base for precision medicine and continue to add value for this patient population. These findings from Early AMPLE have led to the initiation of additional studies in seropositive patients, and reflect BMS's commitment to improving patient care in RA by advancing precision medicine and individualized treatment.

Figure 1. Early AMPLE: a significant new step in advancing precision medicine for RA



Abbreviations: ACPA: Anti-Citrullinated Peptide Antibody; CCP: Cyclic Citrullinated Peptide; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SE: Shared Epitope

Accumulating evidence of Orencia's safety and tolerability

People living with chronic rheumatic diseases require lifelong treatment to prevent disability. Long-term safety and tolerability are therefore important when selecting a treatment. Recent research has increased the understanding of Orencia's acceptable safety and tolerability profile, through the accumulation of longer-term follow-up and studies with greater numbers of patients, across all indications including pediatric populations.

Having been in use for more than a decade, evidence of Orencia's safety has continued to accumulate, based on over 12,000 clinical trial patients and over 750,000 patient-years of treatment in the real world.[33] Importantly, Orencia is approved as a monotherapy and the label does not contain a "black box" safety warning.

Recent evidence has provided greater confidence in the benefit-risk profile of Orencia. Durable efficacy and safety were observed during up to five years of treatment with Orencia in RA following the ACQUIRE trial.[8] A recent pooled analysis of data from nine clinical trials of Orencia – with greater precision and power to identify the safety profile than any of the component trials – found similar rates of adverse outcomes among patients receiving Orencia versus placebo, and identified no new safety concerns.[9] Real-world studies published during 2018-2019 have also demonstrated acceptable long-term safety of Orencia,[34] and lower risks of hospitalized infections and cardiovascular disease with Orencia relative to other biologic treatments. The large numbers of patients included in these real-world studies enabled newly informative assessments of Orencia's safety among clinically important subpopulations with cardiovascular disease or diabetes.[35-37]

The need for demonstrated and well-described safety is especially high for children and young people with pJIA, who are a critical population in need of timely and consistent treatment to prevent potentially debilitating disease progression. Recent analyses of Orencia in extended follow-up from clinical trials and real-world data have demonstrated acceptable safety and tolerability, and improvements in disease symptoms and patient-reported outcomes in patients with pJIA.[38-40]

The increased confidence in and understanding of Orencia's safety profile provided by these studies – which cumulatively provide the largest ever numbers of patients and durations of follow-up studied for Orencia – constitutes newly-recognized value for patients.

BMS's continuing commitment to innovation with Orencia

The findings described above arose from BMS's commitment to furthering understanding of Orencia in collaboration with leading clinical experts. This commitment continues through earlier stage investments as we seek to unlock its potential for additional patient populations, including for small and diverse patient populations with high unmet need. Breakthrough Therapy Designation was granted to Orencia by the FDA in December 2019 for the prevention of moderate to severe acute graft-versus-host disease (GvHD), a life-threatening complication that may develop in patients receiving hematopoietic stem cell transplants from unrelated donors.[41] Orencia is also among the three immune modulators (IMs) selected out of 130 potential candidates for the ongoing phase 3 ACTIV-1 IM trial of safety and efficacy in hospitalized adults with COVID-19 who experience an immune response that can cause respiratory distress syndrome and multiple organ failure.[42] An ongoing phase 3 clinical trial is currently evaluating Orencia's safety and efficacy in idiopathic inflammatory myopathy (IIM).[43] Investments in such research efforts are crucial for advancing medical practice and extending the benefits of existing medications to a diversity of vital patient populations with critical unmet needs.

Conclusion

At BMS, we are focused on developing transformational medicines, like Orencia, that improve upon the current standard of care, and benefit patients, society, and payers. The evidence summarized above has added to the understanding of Orencia's value – and testifies to BMS's commitment to investing in and accelerating the research necessary to optimize the long-term value of Orencia for patient care.

Regarding patient access to Orencia, we are actively engaged in the global dialogue to address out-of-pocket care costs for life-saving medicines and the increased burden they may place on patients, families, and caregivers compared to other health care services. Identifying solutions that provide transformational medicines to patients that help to reduce the overall cost of care to society across the healthcare landscape is a shared goal of the biopharmaceutical industry. Holistic market-based reforms to healthcare infrastructure are the best way to lower costs. We support policies that reduce unnecessary regulations, promote competition, modernize the drug discovery and development process, and enable manufacturers and payers to negotiate innovative and flexible ways to pay for medicines. We will continue the dialogue with stakeholders around the value of Orencia guided by our pricing and access philosophy, and our continued investment in Orencia's potential for patients.

With a unique mechanism of action, Orencia has continued to serve as an effective, safe, and disease-modifying treatment option for people living with RA and pJIA, and more recently for patients with PsA and younger patients with pJIA. We thank ICER for this opportunity to summarize recent evidence of Orencia's value and contribute to the critical discussion of pharmaceutical value, pricing, and investment in innovation that benefits patients.

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Salix's Response (Manufacturer Input Phase III) to ICER's Preliminary Individual Assessment of XIFAXAN® (rifaximin)

When we were notified by ICER of the possible inclusion of XIFAXAN® (rifaximin) in the 2020 UPI report, we agreed to provide evidence supportive of the value of this important treatment option as requested during ICER's Manufacturer Input Phase I & II.

We assembled the most relevant clinical and health economic evidence, including pivotal studies data and substantial real-world evidence. These studies have helped better define the value of XIFAXAN® (rifaximin) in routine clinical practice settings and provide critical validation for the evidence base for this important therapy. Despite the clear utility of this peer-reviewed work, ICER declined to include them as supportive data.

Consequently, we are compelled to highlight our concerns regarding the ICER UPI process. Unlike the previous UPI report, ICER did not request public feedback on its methodology, depriving both manufacturers and the health care providers community from the opportunity to offer valuable commentary on the data most appropriate for consideration in the UPI report. We believe ICER's process is biased in its analysis of the provided evidence in two critical ways that could undermine our health care system.

First, the report arbitrarily excluded key value-based, valid scientific data based on an artificial and rigid standard. Only research published in a narrow date range was considered, an approach that ignores the reality of pharmaceutical research and the development of real-world evidence, in which data sets are often analyzed over time and where publication timelines reflect editorial timelines, and is a poor proxy for when research influences decision making.

Second, the report itself promotes subjective value judgments, declaring increases "unsupported" according to a narrow and arbitrary definition that does not consider or define standards for a "supported" increase.

We are disappointed that our concerns were not considered by ICER, rendering ICER's final report selective, incomplete and unreliable.

To reiterate our concerns that were communicated to ICER during Manufacturer Input Phase II:

The UPI protocol indicates that the intent of the assessment is to determine whether product-specific pricing actions taken by pharmaceutical manufacturers can be rationalized by newly generated clinical data for those products. While ICER clearly assumes that timely developed new clinical evidence is a required justification for pharmaceutical products price increases, ICER's established timeframe is completely inappropriate in the context of evidence development for pharmaceutical products. ICER notes that "reports are not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit based price benchmark.

Instead, we will focus the analysis on whether substantial new evidence exists that could justify its price increase. ICER's approach excludes other considerations that may factor into drug pricing decisions without offering an appropriate rationale and does not allow for full-context consideration of pricing decisions by drug manufacturers. Not having a clear rationale for the relationship between evidence and price significantly undermines the overall quality of the UPI assessment.

Importantly, the limited time range of published data set by ICER for consideration as part of its assessment is restrictive and as a result, excludes several impactful publications of high- quality evidence in support of the value of rifaximin for prevention of recurrence of hepatic encephalopathy (HE) and for patients with irritable bowel syndrome with diarrhea (IBS-D). We disagree with this restrictive approach. As the generation and publication of new evidence for pharmaceutical products require significant time, limiting the timeframe to two years is not realistic and does not accurately reflect the value of the product. The body of evidence continues to evolve over time and needs to be considered holistically. ICER offers no justification or rationale for its approach in the selection of this time frame.

ICER states that "all manufacturer information submitted to justify the price increase will be provided as a component of this report, but any rationales that do not stem from new studies or new analyses will not be evaluated by ICER as a determinant in whether the drug is categorized as having its price increase unsupported by evidence." Therefore, the output of ICER's assessment is a two-category rating system comprised of "price increase with new evidence" or "price increase unsupported by new evidence." This categorization does not allow for "supported price increases with new evidence," and thus, pre-determines the findings and conclusions in a biased manner.

Salix continues to deliver important treatment options to patients and health care providers supported by robust and timely value evidence. We expect to present and publish additional new evidence throughout 2021. We are confident that patients, health care professionals and payers will continue to make important treatment and coverage decisions based on the most current and complete set of evidence, rather than on a review of a small subset of limited evidence that was arbitrarily selected by ICER in the UPI 2020 report.

In the spirit of transparency, a comprehensive list of publications documenting the value of XIFAXAN® (rifaximin) are included below and were referenced in our Manufacturer Input Phase II submission in August 2020. This best provides for an independent and objective review of the supportive scientific findings.

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November 24, 2020

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Boston, MA 02109

RE: Takeda Response to ICER's Unsupported Price Increase (UPI) Preliminary Assessment
Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

Takeda appreciates the opportunity to respond to ICER's UPI preliminary assessment. Takeda believes that the ICER assessment may not adequately reflect the value and benefit of vedolizumab to patients with Inflammatory Bowel Disease (IBD), which that has been demonstrated and reinforced through recent published randomized controlled trials (RCTs), real-world studies, and long-term studies.

ICER failed to incorporate key data associated with price

In alignment with Takeda's pricing philosophy, over the last few years our annual gross and net price changes across our United States portfolio have been and continue to be single digit increases; or in the case of net price change in 2019, negative (-1.6%), which is due in part to the increased cost of rebates paid to insurers and pharmacy benefit managers and discounts paid to other stakeholders. Takeda is one of a handful of companies that provides this data transparently on an annual basis - pricing information for 2019 including average list price change, net price change, and average discount across the portfolio is currently available on our website.

The assessment provided by ICER of the vedolizumab net price increase was incorrect. Takeda has provided the actual data. At the same time, however, several inaccurate assumptions were employed. Over the period 2014 to present, our internal data show that the net price increase of vedolizumab in the U.S. market was less than the overall rate of consumer inflation for the same time frame, which was about 10 percent. For the timeframe of the ICER assessment (2018-2019), the 2.3% net increase was lower than the rate of both the medical consumer price index and overall consumer inflation.

Moreover, ICER noted that total market expenditure of vedolizumab increased over this time to highlight the impact of the price increase. However, total expenditure reflects not only price increases but also changes in the market. During this time period, usage of vedolizumab has increased in response to guidelines updates, which now recommend vedolizumab for induction of remission with moderately to severe active UC patients either before or after anti-TNF therapy,[1,2] including a first-line recommendation over adalimumab in biologic-naïve patients, specifically.[2]

ICER's Review of Clinical Evidence

As part of the assessment, ICER aim to review new evidence for vedolizumab over the prior two years. Whether a price increase is labeled as unsupported hinges on ICER's subjective assessment of the magnitude of clinical effect demonstrated by new evidence. Takeda notes that no transparent criteria are provided regarding differentiation between "small" and "substantial" effects, which dictate whether a price increase is considered supported or unsupported.

ICER concluded that "the VARSITY trial provides high or moderate quality evidence of at least a small increase in net benefit for vedolizumab compared with what was previously known. Given the uncertainties around dosing of the comparator, the effects on corticosteroid-free clinical remission, and around the totality of the evidence as found in ICER's prior network meta-analysis, we do not feel we have high or moderate quality evidence of a substantial increase in net health benefit compared with what was previously known."

Published in the *New England Journal of Medicine*, VARSITY is the first and only completed biologic head-to-head IBD trial, directly comparing and demonstrating superiority of vedolizumab to adalimumab in achieving its primary endpoint.[3] This study simultaneously reflects Takeda's endeavor to address knowledge gaps in the United States and to substantiate the benefit of vedolizumab in the UC population. The results from VARSITY have helped inform healthcare providers as they make treatment choices for new UC patients starting biologics.

Although ICER has acknowledged that the randomized VARSITY trial provided high quality evidence, the UPI report concludes that the magnitude of benefit is small rather than substantial. However, the categorizations of "small" and "substantial" are entirely subjective to ICER. They are not transparent, specific and replicable, and lack of sensitivity analysis to assess the range effect. Without scientific and rigorous evaluation of clinical benefit, safety profile and patient outcomes evaluation, this conclusion is arbitrary. We strongly urge ICER to leave assessment of magnitude of net health benefit to IBD experts, healthcare providers, and patients. Clinical guidelines from IBD professional societies have been updated to incorporate VARSITY trial data,[2] confirming the understood value of this new information within the healthcare community.

The VARSITY study was designed and powered to determine the effect of vedolizumab IV compared to adalimumab SC on clinical remission at Week 52. It is important to note that the corticosteroid-free remission endpoint applies only to a subpopulation of the study--those patients who were on corticosteroids at baseline, and thus represents a subgroup of patients. Furthermore, in the subgroup analyses among patients without baseline corticosteroids or immunomodulators, the treatment effects of vedolizumab versus adalimumab were generally consistent with the results among overall population, indicating that the difference in efficacy was independent of concurrent corticosteroids or immunomodulators use.[3] Neither comparator in the VARSTIY trial (vedolizumab or adalimumab) have approved label in the US to increase doses in treating UC. However, it is occasionally done for both agents (28% for adalimumab and 23% for vedolizumab) in clinical settings.[4] Notably, though, a recent study (SERENE-UC) showed no difference between higher induction regimen (HIR) vs. a standard induction regimen (SIR) of adalimumab.[5]

Regarding the uncertainties ICER mentioned, new or updated clinical evidence published during this timeframe which addressed these uncertainties were included among the 13 references Takeda provided to ICER. Of the 13 documents, ICER excluded 12 from the assessment. Among the excluded trials were real-world evidence that demonstrated vedolizumab to have higher rates of clinical, steroid free, and endoscopic healing than comparators.[6]

Also excluded were long-term results published from the VICTORY Consortium dataset, the largest US-based real-world registry of IBD patients treated with vedolizumab, which showed that clinical remission at 12-months was achieved in over half of all patients.[7,8] The prior ICER network meta-analysis only considered RCTs and therefore did not adequately capture long-term real-world outcomes. Long-term studies are particularly effective in identifying durability of treatment.[9-12] It has been previously demonstrated that early, effective treatments resulting in mucosal healing lowers the risk of colectomy and associated complications,[13] which is value conferred.

In conclusion, a thorough and comprehensive assessment of the value of vedolizumab should take into consideration the previously provided clinical evidence that demonstrates improved efficacy over time and durability of treatment. Assessment of magnitude of benefit to within the therapy area should be transparent and performed by IBD experts. And finally, the price assessment should incorporate the most up-to-date and accurate price considerations.

Takeda believes vedolizumab brings unique benefits to patients with IBD and the US healthcare system. Takeda remains dedicated to achieving this objective through pricing responsibly and working with stakeholders to ensure patient access. Ultimately, we seek to see all products assessed according to their full holistic value to patients and society, and Takeda supports appropriate analyses that incorporate elements that are important to patients and reflect real-world clinical practice

Kind Regards,

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November 24, 2020

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RE: ICER Unsupported Price Increase (UPI) Preliminary Assessment of VIMPAT® (lacosamide) C-V

Dear Dr. Pearson,

UCB has reviewed ICER's preliminary assessment that VIMPAT® (lacosamide) C-V had a price increase from 2018 through 2019 that is unsupported by new clinical evidence. UCB's response will highlight ICER's continued reliance on incorrect pricing data, and the use of an assessment framework that is arbitrary, inconsistent, and non-transparent. To the degree that payers and policymakers consider ICER's conclusions in making formulary and policy decisions that directly impact patient access to medically necessary care, UCB believes that it is critical that the foundational flaws in ICER's approach are fully understood. Without this complete knowledge of the key shortcomings of ICER's reviews, UCB fears that patient access to medicines will be unjustifiably diminished, leading to increased suffering for patients and higher costs to the healthcare system.

As background, UCB is a global biopharmaceutical company with U.S. headquarters located in Atlanta, Georgia. Patients are at the heart of everything we do. With more than 7,500 employees globally, we are inspired by patients and driven by science. Our focus is on innovating new medicines to treat severe, chronic, neurological and immunological conditions. UCB consistently demonstrates our commitment to discovering, developing, and delivering solutions that demonstrate value to patients by annually investing a quarter of our total revenue into the research and development of new therapies.

VIMPAT is a UCB medicine indicated for the treatment of partial-onset seizures and as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older. All indications meet ICER's threshold for review of constituting at least 10% of the use of VIMPAT.

Despite UCB's correction, ICER's inclusion of VIMPAT in the 2020 UPI assessment and its preliminary assessment conclusions are based on inaccurate pricing information.

To conduct its UPI assessment, ICER relies on pricing information generated by SSR Health to discern individual brand drug net price increases during the assessment period. In fact, the entire UPI assessment process—from inclusion selection to the ultimate determination of "price justification"— hinges on this SSR Health data. Therefore, it stands to reason that the accuracy of this data is essential to the validity of ICER's conclusions.

According to SSR Health, as described by ICER in its preliminary assessment of VIMPAT: "Over the 12-month (four quarters) period for which price changes were assessed, lacosamide's wholesale acquisition cost (WAC) increased by 7%, while its net price increased by 10%. This net price change over the

assessed four quarters resulted in an estimated increase in drug spending of $104 million."[i] ICER's data is inaccurate. The actual net price increase for VIMPAT was significantly lower, as shown in the below table:

		2018	2019	Net Price Change	WAC Price Change
ICER/SSR	Net Sales	$969.0	$1,135.0	**10.0%**	**7.0%**
UCB Actual Figures	Net Sales ($M)	$982.4	$1,096.6	**5.6%**	**7.0%**
	Units (M)	2.1	2.2		
	Net Price/Unit	$472.4	$498.9		

UCB provided ICER with this correction in a letter dated July 17, 2020 [see Appendix B]. Despite this correction, ICER has continued to use a net price increase figure that is almost double the actual amount, without acknowledgement or explanation of the discrepancy. We are also providing a copy of this letter to SSR Health to inform them of their inaccurate data.

Even without UCB's correction of the record, ICER should have strongly suspected that SSR Health's data was incorrect on its face. The notion that a brand drug that has been approved and on the market in the U.S. since 2008 in a competitive class would have a net price increase that exceeds (and substantially so) its WAC price increase defies both conventional wisdom and myriad publicly available trend data[ii] [iii] on the "gross to net bubble." Upon seeing this anomaly, ICER should have contacted both SSR Health and UCB to verify the accuracy of the data before forging ahead with the inclusion of VIMPAT in its UPI assessment. Despite UCB's consistent and transparent efforts to provide clarification on this issue, ICER has continued to input a significantly inflated net price increase figure, resulting in VIMPAT being wrongly included in the UPI assessment.

It is important to point out that this is not the first time that ICER has gotten key, foundational data points wrong it its assessments. In fact, in its 2019 UPI assessment, ICER was forced to issue an update to the final report correcting the net price increase data it had relied upon for Genentech's drug Rituxan. ICER explained that this correction was necessary because:

> After publication of the Unsupported Price Increase Report, Genentech provided ICER with exact values for the net price of Rituxan in Q42016 and Q42018, and the volume sold in 2017 and 2018. Due to the discrepancy between the exact values and the data ICER obtained from SSR Health, LLC, ICER decided to update the report with the data provided by Genentech.[iv]

Moreover, ICER was also forced to pull back the entirety of its draft evidence report evaluating the Rheumatoid Arthritis class of drugs in 2019. ICER explained:

> After initially publishing an earlier version of this Draft Evidence Report on September 26, 2019, ICER's internal reviewers identified the need to reevaluate some of the assumptions and calculations in the report to better align our economic modeling with how patients transition between these therapies in the real world.[v]

Prescription drug pricing data, clinical evidence, and the actual practice of medicine in any discreet disease state—and for unique patients—is incredibly complex. UCB appreciates that the task ICER has undertaken to connect and interpret all these complexities is monumentally difficult. However, it is inexcusable and irresponsible for any organization to *knowingly* use incorrect data to inform a model for which the stated goal "is to provide the public and policymakers an explicit and independent approach to determine whether price increases could potentially be supported by new clinical evidence".[vi] Just as ICER corrected the pricing data for Rituxan based on actual data submitted by Genentech, ICER should accept UCB's actual net pricing data, and exclude VIMPAT from this assessment.

Despite UCB's submission of significant new clinical evidence in support of VIMPAT's actual net price increase, ICER arbitrarily excluded every reference provided based on inconsistent and nontransparent interpretations of its inclusion criteria.
According to ICER's 2020 UPI assessment protocol 4.1.2., once a drug is selected for inclusion in an ICER review:

> ICER will then perform independent systematic reviews looking for *new information* from randomized controlled trials (RCTs) over the prior two years on benefits and harms within these indications. However, if manufacturers have submitted evidence, ICER may choose not to perform a systematic review. ICER will not independently look for information other than from RCTs but will assess non-RCT information submitted by manufacturers. Submitted studies may include meta-analyses, economic models, and observational data. Studies reporting patient-reported outcomes and other real-world data will be highly relevant. For information on low frequency harms, evidence from large uncontrolled studies will also be relevant. [*emphasis added*]

Based on this protocol, UCB submitted 25 references to be considered as new clinical evidence supporting VIMPAT's actual net price increase. ICER excluded each and every reference from consideration.[vii] Unsurprisingly, this failure to consider the clinical evidence resulted in ICER making a preliminary assessment that VIMPAT had a (inaccurate) price increase unsupported by new clinical evidence.

Of the 25 references ICER excluded, 8 were arbitrarily excluded based on ICER's explanation that "study was published outside of the timeframe for our review", despite the fact that they produced new evidence during the 2018-2019 review period. However, nowhere in ICER's UPI Assessment protocols does it say that new clinical evidence must be *published* during the timeframe of the review. The protocol simply refers to "new information".

Moreover, in ICER's own press releases, it says: "ICER…evaluate[s] whether there ha[s] been relevant new evidence at any time during the preceding three years that could have supported these price increases."[viii] Again, there is no reference to publication being the key determining factor for inclusion. In fact, ICER explicitly accepts unpublished evidence through its "academic in-confidence" policy[ix], which allows manufacturers to include pre-publication evidence in a manner that protects its confidentiality—a policy which UCB availed itself of during this very review. For these reasons, ICER's decision to exclude the bulk of the new clinical evidence for VIMPAT—most of which was generated, but not yet published during the timeframe for review—is an utterly arbitrary and inconsistent interpretation of its very vague protocols.

Four additional references submitted by UCB to be considered as new clinical evidence were excluded because ICER judged that their "study design does not meet our criteria for assessing efficacy". Three more were excluded due to "previously known information about lacosamide related to safety". The final reference was excluded based on "intervention/comparison not relevant to scope".

UCB has examined all of the protocols for ICER's UPI assessments that the organization has made public, and nowhere does ICER provide manufacturers with any criteria or explanation for what study designs or data are needed to assess efficacy or safety, or to be considered relevant to the scope. ICER's reasons for excluding the remainder of UCB's submissions fail to meet even basic expectations for transparency from an organization that purports to "[take] its obligations to transparency and fairness seriously."[x]

UCB has developed new clinical evidence which supports the accurate net price increase for VIMPAT during the timeframe for review.

As a global leader in the research and development of innovative anticonvulsants for the treatment of epilepsy (hereinafter referred to as anti-antiepileptic drugs, or AEDs), UCB has significant understanding of the condition, the impact of uncontrolled seizure disorders, the challenges that patients experience in achieving seizure control, and the substantial gaps in knowledge about, and treatments for, this debilitating condition.

Epilepsy is a commonly occurring condition. It affects around three million people in the U.S.[xi], making it the fourth most common neurological disorder[xii]. One in 26 people in the U.S. are expected to develop epilepsy at some point in their lifetime[xiii]. Epilepsy is estimated to directly cost $28 billion per year to the U.S. healthcare system [xiv] [xv], with additional indirect costs resulting from the impact on work productivity, employment status, and caregiver burden[xvi] [xvii].

Epilepsy also significantly impacts quality of life for patients and caregivers. Patients with epilepsy often avoid physical activity due to fear of seizures, increasing the likelihood of depressive disorder and neuropsychological dysfunction[xviii]. In fact, individuals with epilepsy have demonstrated higher rates of psychiatric comorbidities, including depression, anxiety, and psychosis[xix], and approximately 24% of people with epilepsy have been diagnosed with a mental health disorder (compared to 11% of those without epilepsy)[xx]. Epilepsy also impacts patients' ability to work[xxi], resulting in people with epilepsy generally earning lower incomes and exhibiting higher rates of unemployment[xxii].

The difference in costs and impact to quality of life between a stable patient with epilepsy and one with uncontrolled epilepsy are vast. According to a 2014 retrospective review of U.S. claims data, the mean annual overall healthcare cost in adult patients with stable epilepsy is $13,839, compared to $23,238 for patients with uncontrolled epilepsy—a difference of $9,399 in additional costs associated with a lack of seizure control[xxiii]. Uncontrolled epilepsy patients also required 54.6% more inpatient visits, and 51.4% more emergency department visits than controlled patients[xxiv].

Achieving complete seizure remission without adverse events and longer-term toxicities is the main goal of epilepsy management.[xxv] [xxvi] The patient journey to find the AED or combination of AEDs to achieve seizure control can be long, complex, and difficult to bear from a medical, financial, and emotional

perspective. Pharmacotherapy is the first-line treatment for epilepsy, with AED monotherapy and/or polytherapy recommended before more invasive alternatives, such as brain surgery or vagus nerve stimulation, are considered[xxvii]. However, despite there being more than twenty AED medications available today, of the three million epilepsy patients in the U.S., one in three's symptoms remain uncontrolled[xxviii].

Given the significant unmet needs for patients with epilepsy (despite the multitude of available AEDs), and the increased costs to payers and the healthcare system associated with uncontrolled seizures, there is considerable value to identifying new AEDs or expanding the label of already-approved AEDs, such as VIMPAT, that can increase the rates of patients with seizure control and stable disease management. For this reason, UCB has continued to invest in significant clinical and innovative research to develop new AEDs and to expand the value of VIMPAT for patients, payers, and the healthcare system.

Further demonstrating UCB's continued investment in improving the lives of individuals living with epilepsy, the FDA this month approved VIMPAT (lacosamide) CV as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients four years of age and older, and VIMPAT injection for intravenous use in children four years of age and older. This new indication underscores UCB's continued commitment to patients on their journey to seizure freedom. As we continue to live through a global pandemic, VIMPAT now gives patients another treatment option to potentially keep them out of the hospital. This new indication epitomizes UCB's demonstrated investment in VIMPAT and epilepsy patients, despite ICER's arbitrary disregard of UCB's submission of clinical information demonstrating VIMPAT's actual net price increase. See Appendix A for more information on UCB's investments into expanding the value of VIMPAT for patients.

Conclusion

ICER erroneously included VIMPAT in the 2020 UPI assessment based on inaccurate pricing data. As such, UCB asserts that VIMPAT should be excluded from this assessment. Moreover, the new clinical evidence that UCB submitted demonstrating the expanded value of VIMPAT was summarily excluded by ICER in a manner which was arbitrary, inconsistent, and nontransparent. UCB asserts that a fair review of the clinical evidence clearly supports the accurate net price increase of VIMPAT during the timeframe of ICER's review.

Sincerely,

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APPENDIX A

- UCB Investments in Vimpat® Demonstrated Improved Clinical Outcomes
  - SP0969 (A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Investigate the Efficacy and Safety of Vimpat® as Adjunctive Therapy in Subjects with Epilepsy ≥4 years to <17 years of Age with Partial-onset Seizures):
    - In January 2019, the U.S. label was updated to report the results of SP0969. These data were reported in sections: 6.1 Adverse Reactions/Clinical Trial Experience and 8.4. Use in specific populations/pediatric patients.
      - Three hundred forty-three patients were randomized; 306 (lacosamide 152 of 171 [88.9%]; placebo 154 of 172 [89.5%]) completed treatment (titration and maintenance). Adverse events (AEs) were the most common reasons for discontinuation during treatment (lacosamide 4.1%; placebo 5.8%). From baseline to maintenance, percent reduction in focal seizure frequency per 28 days for lacosamide (n = 170) vs placebo (n = 168) was 31.7% (p = 0.0003). During maintenance, median percent reduction in focal seizure frequency per 28 days was 51.7% for lacosamide and 21.7% for placebo. Fifty percent responder rates (≥50% reduction) were 52.9% and 33.3% (odds ratio 2.17, p = 0.0006). During treatment, treatment-emergent AEs were reported by 67.8% lacosamide-treated patients (placebo 58.1%), most commonly (≥10%) somnolence (14.0%, placebo 5.2%) and dizziness (10.5%, placebo 3.5%).
      - Additonal post-hoc analysis showed that in children and adolescents (≥4–<17 years) with focal seizures the plasma concentrations of CBZ, LTG, LEV, OXC (MHD), TPM and VPA were not affected by concomitant LCM use, suggesting that no dose adjustment for these AEDs would generally be needed when LCM is added or removed from the treatment regimen. This suggests higher certainty in reaching optimal dose without regimen modification, while achieving seizure control, decreasing the need for doctor visit for titration and dose adjustment, reassuring a) no negative impact on QoL due to potential adverse events, seizures and b) no healthcare resource utilization, and hence costs.

- In a randomized, double-blind, placebo-controlled clinical trial, Vimpat® showed significant and clinically relevant reduction in partial onset seizures in children between the ages of ≥4 and <17. Additionally, this efficacy was established in an uncontrolled partial onset seizure patient population who are on 1 to ≤3 concomitant antiepileptic drugs. This is especially important since Vimpat® utilization overall in the real-world is 85.3% second line use or higher and 60.4% third line use or higher and established efficacy data in this patient population is needed for optimal

treatment decisions. In a post-hoc analysis, this clinical trial further demonstrated that in children and adolescents (≥4–<17 years) with focal seizures the plasma concentrations of background AEDs included in the study were not affected by concomitant Vimpat® use, suggesting that no dose adjustment for these AEDs would generally be needed when Vimpat® is added or removed from the treatment regimen. Reaching the optimal dose quickly secures a well-controlled disease management, helping patients avoid an additional visit to their doctor for dose titration and avoidance of potential adverse events that can lead to discontinuation or increase in seizure frequency. Reducing the need for titration leads to avoidance of negative impact on a patient's quality of life and the economic burden related to healthcare use costs associated with these tangible events, creating new value to patients, payers and the healthcare system.

- In ICER'2 2020 Protocol for UPI, section 3 states that 'new evidence or analyses over the prior two years (beginning of 2018 through the end of 2019) that demonstrates improved clinical or economic outcomes compared with what was previously believed' could be submitted
    - There are no references as to when the data had to be published; however, 4 studies were excluded based on the studies being 'published outside of the timeframe of our review.'
        - Farkas V, Beller C, McClung C, et al. Safety and tolerability of intravenous Vimpat in children with epilepsy: an open-label trial. CNS 2020. 2020: abstract [accepted].
        - Oshima Y, Nakashima K, Hirano K. Safety and efficacy of oral Vimpat as adjunctive therapy in clinical practice: Interim analysis of the post-marketing surveillance in adults with focal-onset seizures. Shinryo to Shinyaku (Med Cons New-Remed). 2020; 57 (2): 98-108.
        - Ruda R, Houillier C, Maschio M, et al. Effectiveness and tolerability of Vimpat as add-on therapy in patients with brain tumor-related epilepsy: Results from a prospective, non-interventional study in European clinical practice (VIBES). Epilepsia. 2020; 61 (4): 647-656.
        - Allard J, Henley W, Mclean B, et al. Vimpat in the general population and in people with intellectual disability: similar responses? Seizure. 2020; 76: 161-166.
- Additionally, ICER states that it 'will not independently look for information other than from RCTs but will assess non-RCT information submitted by manufacturers. Submitted studies may include meta-analyses, economic models, and observational data.
    - An additional 4 studies were excluded with no further rationale than 'study design does not meet our criteria for assessing efficacy', despite the studies reporting out on Vimpat® effectiveness.
        - Hong Z, Du X, Liao W, et al. Efficacy and safety of Vimpat as adjunctive therapy in Chinese patients with partial-onset seizures: subgroup and post hoc analyses of a randomized double-blind trial and open-label extension. Chin J Clin Neurosci. 2019; 27(4): 361-378
        - *Seizures are present in 15% to 95% of patients with brain tumors. Epilepsy is often considered the most important risk factor for long-term disability in patients with brain tumors; however, there are limited data available for the treatment of seizures with antiepileptic drugs (AEDs) in this population. Difficulties in the*

management of BTRE include treatment-resistant epilepsy, the risk of cognitive side effects, and potential interactions between AEDs and chemotherapeutic agents. The use of enzyme-inducing AEDs may accelerate the metabolism of concomitant corticosteroids and chemotherapeutic agents. Guidelines for the management of patients with BTRE therefore advise against the use of enzyme-inducing AEDs and recommend newer generation AEDs as first-choice treatment, to be started after the first seizure. [Ruda et al Epilepsia]

- Ruda R, Hellot S, De Baacker M, et al. Non-interventional study of adjunctive vimpat therapy in patients with brain tumor-related epilepsy. Neurology. 2019; 92(15S): abstract S30.006.
- Ruda R, Hellot S, De Baacker M, et al. Effectiveness and tolerability of Vimpat as add-on therapy in patients with brain tumor-related epilepsy: Results from a prospective, non-interventional study in European clinical practice. Neuro Oncol. 2019; 21 (S3): iii20-iii21.
- Ruda R, Hellot S, De Baacker M, et al. Effectiveness and tolerability of adjunctive Vimpat in patients with brain tumour-related epilepsy: a prospective, non-interventional study in European clinical practice. ILAE-UK 2019. 2019: abstract.

- Four additional references were excluded also due to 'study published outside of the timeframe for our review;' however, for many reasons listed in section 3 of the UPI protocol we believe the references are relevant. The data provided were completed analyses over the prior two years between 2018 and 2019, UCB deems generating efficacy and safety data for new epilepsy indications as relevant, and Vimpat® use in PGTCS [reference burden PGTCS from prior letter as needed] will continue to increase.]
    - These references include:
        - Steiniger-Brach B, Vossler D, Knake S, et al. Efficacy and tolerability of adjunctive Vimpat in the treatment of primary generalized tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. FENS 2020. 2020; abstract.
        - Vossler DG, Knake S, O'Brien TJ, et al. Efficacy and tolerability of adjunctive Vimpat in the treatment of primary generalized tonic-clonic seizures: a double-blind, randomized, placebo-controlled trial. DGfE 2020. 2020; abstract
        - NG YT, Vossler DG, Knake S, et al. Efficacy and tolerability of adjunctive Vimpat in the treatment pf pediatric patients with primary generalized tonic-clonic seizures: subgroup analysis of a double-blind, randomized, placebo-controlled trial. CNS 2020. 2020; abstract [accepted].
        - Vossler DG, Knake S, O'Brien TJ, et al. Efficacy and safety of adjunctive Vimpat in the treatment of primary generalised tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. J Neurol Neurosurg Psychiatry. 2020: [ACCEPTED]

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APPENDIX B

July 17, 2020

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Submitted electronically at: lcianciolo@icer-review.org

Re: Clarification of VIMPAT®'s net price change for ICER's 2020 Unsupported Price Increase Assessment

Dear Ms. Laura Cianciolo,

UCB appreciates the opportunity to provide clarification on Vimpat®'s (lacosamide) CV net price change from 2018 through 2019 as ICER proceeds with its 2020 Unsupported Price Increase Assessment (UPI).

In accordance with section 2.1.6 of the UPI protocol, UCB would like to dispute ICER's estimates used to calculate net price change for Vimpat®'. The correct figures and explanation supporting our analysis are provided below.

		2018	2019	Net Price Change	WAC Price Change
ICER/SSR	Net Sales	$969.0	$1,135.0	**10.0%**	**7.0%**
UCB Actual Figures	Net Sales ($M)	$982.4	$1,096.6		
	Units (M)	2.1	2.2		
	Net Price / Unit	$472.4	$498.9	**5.6%**	**7.0%**

The difference in net price change between SSR Health estimates and UCB actual figures is a result of two key adjustments not reflected in SSR Health.

1) Partial year accounting changes as UCB adopted new international financial reporting standards (IFRS) in Q2 2018: this revision reduces net price change compared to the price in 2018 by 0.5%.
2) Allocating prior period adjustments in financials to the appropriate year reduces price change compared to the price in 2018 by an incremental 3.9%.

Combined, the adjustments referenced above result in a year-over-year in-market net price increase of 5.6% compared to the net price in 2018.

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Today, UCB continues to invest in significant clinical and innovative research to advance and optimize the care of people living with epilepsy. For example, clinical research in assessing the safety and efficacy of Vimpat® in high-risk populations (neonates, newborns, children from one month to < four years of age, pediatrics, and adults) experiencing acute, repetitive seizures and some of the most difficult to treat epilepsies, where today there are no effective treatments for those patients.

UCB will continue to make major contributions to improving epilepsy care and work on addressing key unmet needs in epilepsy through cutting-edge research, increasing our understanding of the impact of social determinants of health on outcomes, and using real world data to pave the way for better outcomes for those living with epilepsy.

Please feel free to contact Eddie Lee, PharmD, Senior Director, U.S. Health Economics and Outcomes Research (HEOR) with any questions you may have on the responses provided.

Sincerely,

Patricia A. Fritz
Vice President, U.S. Corporate Affairs
UCB, Inc.
Patty.Fritz@ucb.com